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BUREAU OF HYGIENE AND TROPICAL DISEASES.

TROPICAL DISEASES BULLETIN.

Vol. 43.] 1946. [No. 5.

SUMMARY OF RECENT ABSTRACTS.*

IV. TRYPANOSOMIASIS.

African Trypanosomiasis.

Epidemiology.

MacKichan (p. 13) reports an outbreak of human sleeping sickness in Uganda in which, during the period 1940-1943, there were 2,432 known cases and 274 deaths. The outbreak was declining when the author wrote the paper. Clinical and experimental evidence indicated that the trypanosome concerned was *T. rhodesiense*, and the author states that this organism has not, apparently, been isolated previously in Uganda [but Duke (p. 13) writes that it was found several years ago]. One of several volunteers was infected with trypanosomes which were passed through rats from wild-caught *Glossina pallidipes*. The outbreak was probably due to the introduction of infection by labourers brought from Tanganyika Territory.

Ceccaldi (p. 710) reports on sleeping sickness in French Equatorial Africa.

Aetiology.

van Hoof *et al.* (p. 96) quote the arguments which support the view that *T. gambiense*, *T. rhodesiense* and *T. brucei* are biological races of a single species rather than independent species. To distinguish between them these authors have studied the forms present in the salivary glands of infected tsetse flies, and have concluded that the distribution, relative numbers and dimensions of the various developmental forms, in the salivary glands, provide a ready means of differentiation between *T. gambiense* on the one hand and *T. rhodesiense* and *T. brucei* (which are indistinguishable) on the other. These differences are set out in tabular form, for which the original abstract should be consulted. In comment, Hoare remarks that since the differences between the two subgroups are purely relative, the three species of polymorphic trypanosomes must still be regarded as morphologically identical, and he notes that certain facts mentioned by the authors appear to be contradictory.

Stefanopoulo and Étévé (p. 258) have shown that a strain of *T. gambiense* previously reported by Roubaud and Provost to have neurotropic properties

* The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1945, v. 42. References to the abstracts are given under the names of the authors quoted and the pages on which the abstracts are printed.

for mice does, in fact, produce meningo-encephalo-myelitis in these animals. It had previously been thought that mice showed blood infection only.

RODHAIN and VAN DEN BERGHE (p. 872) have succeeded in infecting chick embryos with certain spirochaetes, leishmania and trypanosomes. Most of the pathogenic organisms grew in the embryos, but all the non-pathogenic organisms failed to do so.

Transmission.

BAX (p. 702) reports on the work of the Tsetse Research Department (Tanganyika Territory) since February, 1944. The items of work done are too numerous to be recapitulated here, and the original abstract should be consulted for details. Mention may, however, be made of an attempt to oust *G. swynnertoni* by introducing into its habitat large numbers of pupae of *G. morsitans*. The latter fly soon outnumbered the former, and some hybrids were caught, but it is too soon to know if the experiment was successful.

POTTS (p. 98) reports an attempt made at cross-breeding between *G. morsitans* and *G. swynnertoni*. A few hybrids were obtained, and some of these hybrids (females) were fertile after insemination by *G. morsitans* or *G. swynnertoni*. Further matings did not produce offspring. Cross-mating seems to occur less readily than mating within the species [but see VANDERPLANK, below], but the evidence suggests that the introduction of large numbers of pupae of an alien species into country where the indigenous species is not plentiful, may lead to cross-mating and the production of relatively few, and infertile, offspring. This is a possible method of tsetse control. VANDERPLANK (p. 99) gives a table of the cross-mating which he has effected between *G. morsitans* and *G. swynnertoni*. Insemination occurred as readily in the cross-matings as with the same species where no choice was offered, but the cross-matings produced far fewer pupae. The author brings out the point that a few hours after a female is inseminated "she is no longer attractive to males, and will not permit further coitus."

JACKSON (p. 186) has continued his observations on a *G. morsitans* population, and has confirmed his finding that dispersal consists largely of movement within ambits governed by vegetational boundaries, which are rarely more than half a mile in radius. It appears that a catch of one "old" male fly per 10,000 yards represents a population of some $7\frac{1}{2}$ "old" males per square mile, and perhaps twice as many females. The author discusses the factors which bear on these conclusions and which must be taken into account in computing results.

CHORLEY (p. 98) has found *G. palpalis fuscipes* breeding as far as 12 miles from water, in dense humid forest broken up by elephant tracks. He thinks that the general limitation of the fly to waterside areas is determined, not by food supply (which exists elsewhere), but by climatic conditions of shade and humidity.

In the Uganda outbreak MACKICHAN (p. 13) found three species of *Glossina*:—*G. pallidipes* (the chief, if not the only, vector in the area), *G. palpalis fuscipes* (which breeds in evergreen forest as far as 10 miles from water) and *G. brevipalpis*.

WILLIAMS (p. 14), in one small experiment in Portuguese East Africa, found that *G. pallidipes* was most active in the evening and early morning. BURTT (p. 868) shows that *G. pallidipes* which have hypertrophied salivary glands appear to be particularly suited to the development of trypanosomes, especially *T. brucei*.

JACKSON and VANDERPLANK (p. 187) have measured the diameters of red blood cells of about 40 species of East African mammals. There is considerable difference between species, but closely related species have cells of about

the same size. The work was done in relation to the animals on which tsetse flies feed.

POTTS and VANDERPLANK (p. 869) give their reasons for the opinion that contact insecticides (pyrethrum and DDT) are absorbed through the pulvilli of tsetse.

GASCHEN (p. 453) has written a monograph on the tsetse flies of French West Africa.

Clinical Findings.

In a description of sleeping sickness as it is seen in Tanganyika Territory, FAIRBAIRN (p. 452) makes the point that this infection (by *T. rhodesiense*) can always be diagnosed by blood examination, that gland puncture is unnecessary, but that in some advanced cases diagnosis can be made more quickly by lumbar puncture. Prognosis depends greatly on the protein content of the cerebro-spinal fluid, and can be estimated from observations made over a period of some months. Treatment with Suramin (Bayer 205) need not be stopped on account of albuminuria, but vision should be tested before each dose of tryparsamide. In relapses, repeated courses of tryparsamide should be avoided because of the danger of making the trypanosomes arsenic-fast, and because of the risk of producing optic atrophy. Monthly doses of Suramin may be given to keep the blood free from trypanosomes. The author argues against the use of Suramin as a prophylactic, since there is a real danger of " cryptic " infection ; it is preferable for the individual to get a definite attack which can easily be diagnosed and cured.

A case of Gambian sleeping sickness in a British soldier who had served in Nigeria some years before is reported by GRANT *et al.* (p. 187). The diagnosis was not made until 2½ years after the probable time when the infection was contracted. This case illustrates the difficulty of diagnosis sometimes experienced in this infection, and points to the importance of keeping in mind the possibility of sleeping sickness in returned soldiers. Referring to the paper by Grant *et al.* above, and to the diagnostic methods that had been used by the various medical men who had examined the patient, HARDING and HAWKING (p. 188) show that the well-known procedure of gland puncture might have been used with advantage, and that blood culture is a simple and practical method, which may give positive results when other tests are negative.

FAIN (p. 14) found trypanosomes in material from sternal puncture in 11 of 20 patients with clinically advanced disease but in whom blood and gland juice (except in one instance) were negative. This method of examination is therefore useful.

SIEYRO NIETO (p. 15) has made investigations on the blood picture, the coagulation time, the serum calcium and on various tests with the cerebro-spinal fluid in trypanosomiasis as it was seen in Fernando Po. For the last he thinks the cell count more useful than the total protein figure, but there may be an abnormal colloidal gold reaction in the absence of abnormal cell count or total protein, and this may be the only sign of involvement of the central nervous system.

VAN GOIDSENHOVEN and SCHOENAERS (p. 791) describe the preparation of an antigen suitable for the complement fixation test in trypanosomiasis.

RODHAIN and VAN GOIDSENHOVEN (p. 869) have shown that the complement fixation test (in which an antigen prepared from *T. equiperdum* is used) tends to remain positive in man and in animals for some years after clinical cure. A positive test is not an indication for the continuation of treatment.

Treatment.

FOWLER (p. 541) has treated 42 cases of Gambian sleeping sickness with tryparsamide administered by intravenous drip, the dose being 2 gm. daily

(in 2 pints of double-distilled water, which take 8 hours to give) for 6–9 days, with an interval of one day in the middle of the course. This treatment causes high fever and exhausts the patients; it may have been partly responsible for death in the seven subjects who died. Nevertheless, in spite of the fact that there was evidence of involvement of the central nervous system in most of the patients, the immediate results were good in those who survived, and in patients observed for several months the improvement was maintained.

EAGLE (p. 354) reports that γ-(p-arsenosophenyl)-butyric acid has been tried in human sleeping sickness in West Africa, and that the results in early cases are satisfactory, cure being achieved within two weeks by daily injections of about 0·4 mgm. per kgm. body weight. It is ineffective in late cases and may cause toxic encephalitis in such patients.

KING (p. 971) discusses the chemical structure of arsenicals, and drug resistance of trypanosomes. The paper is highly technical, and details should be sought in the original abstract.

HAWKING (p. 971) has found that at 37°C. living trypanosomes absorb a large amount of stilbamidine, but that dead trypanosomes do not absorb it in any appreciable amount. Evidence was obtained that trypanosomes in the blood of animals absorb the drug *in vivo* when it is injected into the animals. SAUNDERS *et al.* (p. 354) have followed up a number of patients with Gambian sleeping sickness, treated with pentamidine. The results suggest that those whose cerebrospinal fluid contains less than 30 cells per cmm. are usually cured, but that in those with more than 30 there is usually relapse. In very advanced cases the drug is useless.

Control.

In a paper on recent progress in the control of sleeping sickness in Nigeria, LESTER (p. 788) makes the point that the disease assumes different forms—mild, toxic, or nervous—and that the mild form is the most common. At the height of the epidemic, some years ago, teams were formed to give mass treatment, but the author thinks that where the incidence of the disease is reduced to about 1 per cent., the permanent treatment centres now established will be in a position to detect any outbreak and to deal with it. Great success has attended the work of the mass treatment teams. River clearing has been successful in eliminating the riverine tsetse from large areas, and the Anchau corridor of 480 square miles is now free from fly.

In the report on the medical services of Nigeria for 1943 (p. 790) it is stated that there was no evidence of any general increase of sleeping sickness in that year. At the permanent treatment centres, not only sleeping sickness but other diseases also are dealt with.

HUNT and BLOSS (p. 969) state that sleeping sickness has never been eliminated from part of the Sudan which adjoins French territory. They have attempted control by instituting a modification of SYMES's block method, to deal with *G. palpalis fuscipes*, the only vector. This has been very successful. BLOSS (p. 969) describes an outbreak of sleeping sickness near Meridi in the Sudan, which was controlled by the block method and by the creation of rod clearings along the streams haunted by *G. palpalis*. Each method possesses its own advantages. He found that the disease could establish itself even where the fly density was low, and contends, therefore, that fly control must be thorough. The infection was of the Gambian type.

TRYPANOSOMIASIS OF ANIMALS.

General.

BROWAEYS (p. 189) has infected mice with single trypanosomes from a strain of *T. brucei* maintained in Paris. The incubation period was usually

longer than when several trypanosomes were injected, but the duration of the disease was not, apparently, related to the dose.

FIENNES *et al.* (p. 791) describe the course and pathology of *T. congolense* disease of cattle. VANDERPLANK (p. 703) has succeeded in infecting *G. longipennis* and *G. fuscipleuris* with *T. congolense*, and has found one female *G. austeni* infected in nature with the same trypanosome.

KUBES (p. 454) has written a monograph in which he compares Venezuelan and African strains of *T. vivax*.

SEAGER (p. 261) has succeeded in infecting ducks by injection of *T. equiperdum*, and refers to the possibility that there may be avian reservoirs of similar mammalian parasites. In comment, CORSON states that human and other mammalian pathogenic trypanosomes have successfully been transmitted to various species of birds, and that avian blood has been found in nature in tsetse flies. CHEN *et al.* (p. 872) report observations on parasitaemia and length of survival of mice infected with *T. equiperdum*.

VAN DEN BERGHE (p. 871) has investigated the infection of chick embryos with *T. evansi*; for details the original abstract should be consulted.

ROMAÑA (p. 873) reports on the infection of bats with *S. vespertilionis*.

Treatment.

CALVER (p. 704) has written a thesis (unpublished) on chemotherapeutic studies in experimental *T. congolense* infections. This has been very fully abstracted. Two strains of the trypanosome were used, which differed in pathogenicity and in the course of the infections they produced. The author distinguishes between acme strains (passaged from mouse to mouse at the point when the trypanosomes first become uncountable in the blood), and relapse or chronic strains (passaged at a later stage of the infection). Treatment was given at various stages of the disease, and for this the author used certain compounds of the phenanthridinium series, Stilbamidine and quinoline methochloride. The details of these treatments cannot be summarized more satisfactorily than in the original abstract; the results indicate considerable value for several of the compounds tested. Attempts to produce drug-fastness were not successful. The immunity developed after infection and cure differed in the two strains, and was complex even in relation to the homologous strain; there was no cross-immunity between the strains. Field trials in Africa with two of the phenanthridinium compounds have been reported, and these, together with the author's own work, indicate that the drugs are likely to be useful. BROWNING *et al.* (p. 258) have found that one of the series of phenanthridinium compounds has a curative action in *T. congolense* infections of mice, at a dosage much less than the maximum tolerated dose. BROWNING and CALVER (p. 259) have taken this work further, using two strains of *T. congolense* with somewhat different characters. Treatment was more effective when the trypanosomes were abundant than earlier, which suggests that immunity may play a part in the cure. Immunity after cure was much more solid with one strain than with the other, and there was no cross immunity. In the field, results may depend on the strains of *T. congolense*, the stage of infection and other factors. CARMICHAEL and BELL (p. 259) have tested this drug in *T. congolense* infections of cattle, and advise that it should be given intravenously or intramuscularly. Most of the animals relapsed, but retreatment was largely successful. Details are given in the original abstract.

A new phenanthridinium compound prepared by BROWNING was tested in cattle, infected with *T. congolense*, by CARMICHAEL and BELL (p. 260) in Uganda. The results were very good, and cure was obtained in all cases. The subcutaneous route of administration is apparently favoured, and though toxicity was not investigated, it is believed to be low.

WALLS *et al.* (p. 709) contribute a note on the relationship between structure and trypanocidal properties in compounds of the phenanthridine series.

EAGLE *et al.* (p. 15) have made extensive studies on a large series of phenyl arsenoxides in the treatment of trypanosome infections of mice and rabbits, and in spirochaetal infections. The most promising compound was the *p*-butyric acid derivative of phenyl arsenoxide, which has a favourable chemotherapeutic index. EAGLE and MAGNUSON (p. 356) report that a strain of *T. equiperdum* spontaneously became resistant to phenyl arsenoxides, in the absence of drug treatment. They discuss the mechanism of drug resistance, and suggest that a drug may act simply as a factor which allows a spontaneous variant to become apparent, by killing off the more susceptible organisms.

Working with mice infected with *T. equiperdum*, CHEN *et al.* (p. 869) found that the trypanocidal activity and toxicity of trivalent antimonials were greater than those of pentavalent antimonials. The therapeutic index of the pentavalent compounds was higher than that of the trivalent. Cysteine, injected at the same time as these drugs, reduced both the toxicity and the trypanocidal action of the trivalent, but not of the pentavalent, compounds.

BRAUSS (p. 355) writes of the value of Surfen in *T. brucei* infections of mice. It is a useful trypanocide, but not so good as Germanin. It is ineffective against *T. congolense.*

BESSEMANS *et al.* (p. 870) show that penicillin has no action on *T. congolense* either *in vitro* or *in vivo.*

CHAGAS'S DISEASE.

ELKELES (p. 872) criticizes the generally accepted views of the development of *T. cruzi*; details of his findings cannot be given here. The methods and deductions are themselves criticized in a comment by HOARE.

ROMAÑA and MEYER (p. 972) have cultivated *T. cruzi* in cultures of chick embryo tissues, in which the trypanosome grew readily. They were able to follow the complete cycle of development of the parasite in all its well-known stages.

ROMAÑA (p. 974) describes the course of infection in rats in which metacyclic forms of *T. cruzi* had been applied to areas of scarified skin.

WOOD (p. 710) shows that *T. cruzi* may remain alive in dead Triatomid bugs for several weeks or months. He considers that this fact is important in maintaining a large rodent reservoir of infection, since rodents feed on bugs, especially, perhaps, dying bugs. No trypanosomes were found in mites parasitic on infected bugs. WOOD (p. 710) notes that in California *T. cruzi* has been found in *Triatoma protracta*, in a single example of *Neotoma fuscipes macrotis*, and possibly in a bat. TORANZOS (p. 874) writes on the infection of *Triatoma rubrovaria* by *T. cruzi* in Argentina. NERY GUIMARÃES and JANSEN (p. 972) have found a new vector of *T. cruzi*, which LENT (p. 973) has named *Parabelminus carioca.*

In preliminary work on the action of DDT on Triatomid bugs, LENT and DE OLIVEIRA (p. 973) found that the action was slow, and that bugs are not so susceptible as some other arthropods.

LUIS DAO (p. 17) notes that spleen puncture is useful in the diagnosis of Chagas's disease.

MAZZA *et al.* (p. 792) describe in detail the histopathological changes found in biopsy specimens of the conjunctiva in the first stage of Chagas's disease. The findings cannot further be summarized. COUCEIRO (p. 975) describes a neuritis, predominantly interstitial, which arises in dogs infected with *T. cruzi.* DAO (p. 711) reports two cases of sudden death in Chagas's disease. ROMAÑA and COSSIO (p. 874) discuss the chronic cardiac conditions found in Chagas's disease.

An antigen prepared from *T. cruzi* has been used by ROMAÑA and DIAS (p. 974) for the complement fixation reaction in Chagas's disease. The test is generally positive, but may also be positive in cutaneous leishmaniasis, though it is negative in syphilis, malaria and certain other diseases. MUNIZ and DE FREITAS (p. 975) have used the Davis antigen for the complement fixation test. This is satisfactory and the test is a reliable diagnostic procedure. The agglutination test is usually positive, at high titre, in Chagas's disease, but may be positive, though at much lower titre, in certain other diseases.

NEGHME (p. 453) found that penicillin had no favourable effect in *T. cruzi* infections of mice. *Charles Wilcocks.*

MALARIA.

MACNAUGHT, W. W. **Primary Benign Tertian Malaria among British Troops in Normandy.** *Brit. Med. J.* 1946, Feb. 16, 236–7.

Records are given of eight cases of *P. vivax* malaria among British soldiers who served in Normandy during August and September 1944. None of these patients had previously been outside the United Kingdom, and it appears certain that infection was acquired in Normandy in each case. Many other apparently primary infections were noted, but as the patients in question had previously served in malarious countries the evidence of infection in Normandy was not conclusive.

In all eight cases the diagnosis was made by blood examination; clinical diagnosis was not always easy, for at that time numerous patients were being admitted to hospital with febrile symptoms due to acute intestinal infections, infective hepatitis or the " effects of heat ".

Anopheles maculipennis is found in Normandy, but it is very long since indigenous malaria had been reported from the locality in question. Some of the German troops who had been stationed there had had earlier service in Africa and many of our own invasion force had served in malarious regions. Either or both of these sources may have been responsible for the infection of the Normandy *Anopheles.*

[An interesting study, by BRUMPT, of anophelism without malaria, and the spontaneous regression of malaria (this *Bulletin*, 1946, v. 43, 4) reports numerous cases of locally acquired malaria in places that have long been free from the disease which formerly afflicted them. In some such places the regression began by a diminution in the number of gamete carriers, in part attributable to the use of quinine. The introduction of fresh gamete carriers during the war resulted in the reappearance of indigenous malaria.] *Norman White.*

YAO, Y. T. **Synopsis of the Epidemiology of Important Parasitic Diseases in China. Part I. Malaria, with Keys to the Chinese Anopheline Mosquitoes.** *Chinese Med. J.* (Chengtu Edition.) 1945, Apr., v. 63A, No. 3, 103–26. [59 refs.]

The author condenses into small space all published information regarding the distribution of malaria in China. Spleen rates and parasite rates disclosed by malaria surveys in the various provinces during the last 14 years are brought together in tabular form. A list of the 37 species of *Anopheles* that have been found in China is amplified by information concerning the geographical distribution of each species. Another table gives the results of mosquito dissections that have been reported, from which it appears that seven species are responsible for malaria transmission, *A. minimus*, *A. jeyporiensis* var. *candidiensis*, *A. maculatus*, *A. hyrcanus* var. *sinensis*, *A. pattoni*, *A. maculipennis*

var. *atroparvus* and *A. sacharovi* (the last two on epidemiological grounds). Finally there is a key designed to facilitate the identification of Chinese anophelines. *Norman White.*

HUFFAKER, C. B., SOTO, H. & REY, H. **Additional Wild-Caught *Anopheles punctimacula* D. and K. infected with Malaria Plasmodia in Colombia, South America.** *Amer. J. Hyg.* 1945, Sept., v. 42, No. 2, 107–10. [12 refs.]

The scanty evidence upon which was based the conclusion that *Anopheles punctimacula* D. and K. is "incapable of transmitting malaria," is briefly mentioned. It amounts to failure to demonstrate malaria plasmodia in 18 mosquitoes after feeding on infected persons.

Since 1936 three natural infections have been reported; the present authors record five more. In February 1944, they collected adults from houses and in June the same year from houses, stables and baited traps. They supplied the females with 10 per cent. sucrose and kept them alive at 72°F. for from five to eight days before dissecting them. The stomachs only were then removed and stored in 50 per cent. alcohol until they could be stained and examined.

In three stomachs, very small cysts were seen which would easily have been missed if the females had not been kept alive for some time after capture. Altogether, out of 433 stomachs, five were found to be infected (1·2 per cent.), but these all occurred in the June dissections (326), which gives an infectivity rate of 1·5 per cent.

The authors conclude that *Anopheles punctimacula* must not be ignored as it may be a dangerous vector of malaria wherever it is produced in abundance. *H. S. Leeson.*

ROGERS, K. B. **Concentrating Malaria Parasites in Thin Films.** *Brit. Med. J.* 1946, Jan. 5, 11–12.

The author describes a technique which he has devised for concentrating malarial parasites for the purpose of facilitating diagnosis. It involves centrifugation in a small tube followed by removal of the packed red cells and some serum in a capillary tube. This tube is centrifuged (2,000–3,000 revolutions) for 20 to 30 minutes. The top portion of the packed red cells is cut off with a little of the supernatant serum. This piece of capillary tube open at both ends is inserted into a specially constructed pipette which has an S-shaped bend to prevent the tube passing to the closed lower end of the pipette. The pipette with the tube in it is centrifuged for 2 to 5 seconds. The blood and serum are driven out of the capillary tube to the closed lower end of the pipette. On cutting off the tip of the pipette the red cells and serum can be blown on to a slide for film making. It is claimed that a concentration of from 5 to 56 times can be obtained. Of 52 positive bloods five were positive only in the concentrated blood film. Those interested in the technique must consult the original paper for further details. *C. M. Wenyon.*

METCALF, R. L. **The Detection of the Plasmodia of Human Malaria in Blood Films by Fluorescence Microscopy.** *J. National Malaria Soc.* Tallahassee, Fla. 1945, Sept., v. 4, No. 3, 223–9, 3 figs.

The paper describes a method of identifying malarial parasites by means of the fluorescence microscope. Thin blood films fixed in methyl alcohol are stained with berberine sulphate or rivanol. When such films are observed under the fluorescence microscope the malarial parasites are luminous, and are thus easily detected. It is claimed that the appearances of the three species

of parasite are much like those seen in Giemsa preparations, except for the colour differences. The author suggests that because of its simplicity the method may be of value in routine malaria surveys. Similar observations have been made previously by Bock and Oesterlin and by Patton and Metcalf [this *Bulletin*, 1944, v. 41, 545 and 546]. *C. M. Wenyon.*

Shute, P. G. **Diagnosis of Malaria : Notes on the Preparation and Staining of Thin and Thick Blood Films, for the Detection of Malarial Parasites.** *Monthly Bull. Ministry of Health & Emergency Pub. Health Lab. Service (directed by Med. Res. Council).* 1946, Feb., v. 5, 32–6.

Kleeberg, J. **Studies on the Weltmann Reaction in Malaria Cases.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1945, Dec., v. 39, No. 3, 221–8, 1 fig. [36 refs.]

The Weltman Coagulation Reaction is an entirely unspecific protein-globulin reaction, but the author considers that it might be of considerable diagnostic value in tropical fevers. The test consists in the addition of 0·1 cc. of haemoglobin-free serum to each of a series of ten small test-tubes containing graduated ascending dilutions of calcium chloride solution. The tubes are shaken and placed in a boiling water bath for 15 minutes ; the reaction is then read. The contents of the tube may be clear, faintly opalescent, turbid or there may be flocculation. The number of tubes in which flocculation occurs is called the coagulation band. In normal serum the first six tubes usually show flocculation : coagulation values of 6 or 7 are " normal." If coagulation occurs in tubes with higher dilutions of calcium chloride (tubes 8, 9, 10), this " shift to the right " of the coagulation band is indicative of a chronic proliferative process. If there is a shortened coagulation band (tubes 1 to 5 only) such " shift to the left " is indicative of an acute inflammatory exudative process.

The author reports on the results of the test in 25 cases of malaria. Though a malaria attack clinically produces all the features of an acute inflammatory process, the W.C.R. showed a shift to the right in 13 cases, was normal in 10, and a shift to the left in 2 only. Haemolysis may be responsible for the lengthened coagulation band in malaria. The test is particularly valuable in all haemolytic processes ; it might be helpful in blackwater fever. The test repeated during the course of a disease may be helpful in prognosis.

A succinct description of the technique is given. *Norman White.*

Plötner, K. Ueber die Ursache der Regelmässigkeit des Malariafiebers. [**The Cause of the Periodicity of Malarial Fevers.**] *Deut. Tropenmed. Ztschr.* 1944, Apr.–May, v. 48, Nos. 7/10, 148–56, 5 figs.

In three cases of malaria, intercurrent infections which gave rise to continuous fever during the otherwise apyrexial periods between paroxysms resulted in the disappearance of the malarial fever and parasites.

In a patient suffering from quotidian paroxysms after subcutaneous administration of blood containing benign tertian parasites, artificial fever was induced, during an apyrexial period, by intravenous injection of vaccine. After an apyrexial stage of two days following this artificial fever, the periodicity of the malarial paroxysms became tertian and, according to the author, " one generation of parasites " disappeared from the peripheral blood. In two cases of sporozoite-induced therapeutic benign tertian malaria, however, artificial fever had no effect.

The author suggests that an approximate 12-hour period of normal temperature is favourable to the development of *P. vivax* and *P. malariae.* Artificial

fever induction might be useful in conjunction with chemotherapy in frequently relapsing cases. *B. G. Maegraith.*

LAHA, P. N. **Malarial Nephritis with an Illustrative Case Report.** *J. Indian Med. Ass.* 1945, Nov., v. 15, No. 2, 46–7 & 43.

ANN. TROP. MED. & PARASIT. 1945, Dec. 31, v. 39, Nos. 3/4, 137–8. **Malarial Research leading to Paludrine.** [Editorial.]

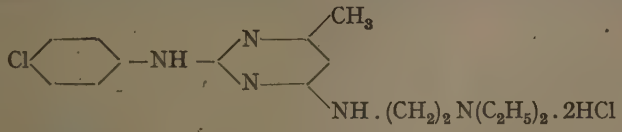
CURD, F. H. S., DAVEY, D. G. & ROSE, F. L. **Studies on Synthetic Antimalarial Drugs. I. Biological Methods. II. General Chemical Considerations.** *Ann. Trop. Med. & Parasit.* 1945, Dec. 31, v. 39, Nos. 3/4, 139–56, 1 graph. [17 refs.]; 157–64. [12 refs.]

In the Editorial Notice a brief outline is given of the researches leading to the synthesis of the new antimalarial drug Paludrine by the Imperial Chemical Industries Limited at Blackley, Manchester, and of the early clinical trials carried out by the Liverpool School of Tropical Medicine. This work owed a great deal to the initiative and vigour of the late Professor Warrington YORKE who gave much of his time to its welfare. The issue of the *Annals of Tropical Medicine and Parasitology* in which these researches are recorded is dedicated to his memory.

I. In this paper, written nearly two years ago, the authors deal briefly with the life-cycle of malarial parasites from the point of view of chemotherapy, in the light of recent knowledge resulting from intensive studies on bird malaria. Thus a drug may act on the sporozoite stage, on the succeeding developmental forms named cryptozoites by HUFF *et al.* [this *Bulletin*, 1943, v. 40, 815; 1945, v. 42, 538] and referred to as the tissue phase by DAVEY [this *Bulletin*, 1944, v. 41, 365] or finally on the blood forms of the parasite, which are of most interest to the clinician. Whereas in the past drugs were tested against blood-forms, as in the well-known method of ROEHL, which is discussed, JAMES has long emphasized the need for a causal prophylactic which would be effective against the early stages of the parasite. It should not, however, be forgotten that pamaquin and possibly mepacrine were discovered by Roehl's technique. Soon after the introduction of sulphonamides it was shown that certain members of the group had a degree of specificity against human malaria parasites which, however, was not manifested against *P. relictum* by the Roehl test. The authors decided to use in their test acute *P. gallinaceum* infections in chickens on account of its practicability and the fact that this parasite was, in line with the human parasites, sensitive to certain sulphonamides as well as to the standard antimalarials, quinine, pamaquin and mepacrine. Cross checks on activity were also made on *P. lophurae* infections in ducks, and on *P. cathemerium* and *P. relictum* infections in canaries to determine any specificity of action. The exoerythrocytic forms found in *P. gallinaceum* infections did not interfere with the test for suppressive drugs on account of the acute nature of the treated infection. In the test which resembles that employed by American workers, chicks, six days old, were inoculated *via* a jugular vein with 0·2 cc. of a suspension of parasitized cells containing 40–50 million parasites, from a donor chick with acute infection. Parasites are demonstrable in the blood from the time of inoculation and a peak of parasitaemia occurs approximately four days later. In treating the established blood infection, the drug was given orally by catheter in 1 ml. of fluid about 3 hours after inoculation and twice daily on the three following days. In order to assess the activity of an unknown drug, comparison was made of the density of infections in six chicks treated with it, in six others treated with mepacrine, whose potency was known, as well as

in the same number of untreated controls, at the time when the peak of parasitaemia occurs in the latter. It emerged from the author's experimental work with mepacrine, in agreement with earlier writers regarding quinine, that there was a critical dosage range for this drug. A critical dose was established for each drug tested and compared with the standard mepacrine. The authors regard the critical dose as of the greatest importance, it is defined as " the minimum dose of a substance which, administered according to a particular dosage schedule, exerts what is materially the maximum effect of the drug." Other factors were also considered in the case of a new drug such as toxicity for mammals, action against other plasmodia and possible specificity of action, an interesting case of which is described, before clinical tests were made on man. In this connexion, their experiences with the drugs 2666 and 3349 (see below) are described. Whether a drug active in *P. gallinaceum* infection will be active in human malaria or whether different drugs given under a similar dosage schedule are absorbed to the same extent, cannot be foretold. Nevertheless, the test employed has led to the discovery of new and potent antimalarials.

II. The authors state their two main objectives to be the discovery of a true prophylactic drug in malaria and of other drugs more potent than existing types for use in clinical practice. The approach to the latter problem is described in this communication. Following the discovery of pamaquin and mepacrine, which contain respectively a quinoline and an acridine nucleus, synthetic work has centred mainly on derivatives of these types, although other heterocyclic ring-systems have been studied. A drug more potent than mepacrine was not, however, discovered. The presence of basic side-chains attached to the different ring systems was shown to be of great importance for antimalarial activity by the work of SCHULEMANN and collaborators. The present authors have devoted their attention to certain derivatives of pyrimidine. Substances containing this ring-system are often of great physiological importance. Derivatives of molecular weight 300–400 containing a substituted phenyl group and basic side-chain were found to be inactive in *P. gallinaceum* infections, whereas the corresponding anilino pyrimidines of which 2666



was an example, showed antimalarial activity, which persisted in spite of wide variations of the prototype. As stated by the authors " The prerequisite for antimalarial activity therefore appeared to be the simultaneous association with the pyrimidine nucleus of not only a basic alkylamino group but also an aryl group linked through a grouping capable of prototropic change." When the—NH—linkage of the above compound was replaced by a guanidine group —HN—C—NH—the compound 3349 (2-*p*-chlorophenylguanidino-4-β-diethy-
‖
NH
laminoethylamino-6-methylpyrimidine) was obtained, which was active in bird malaria and the three common forms of human malaria, when used as the dihydrochloride. This substance also offers possibilities of tautomeric change similar to those of 2666 above, with which antimalarial activity may be associated, a view which is discussed in relation to possible tautomeric changes in mepacrine. Certain views of others on the mode of action of this powerful antimalarial are given. The present authors believe that the pyrimidines 2666 and 3349 may undergo corresponding degradation changes *in vivo* and give

rise to compounds with marked similarities to riboflavin. Work is in progress to elucidate the mechanism of antimalarial action of these new substances and their possible relation to the yellow enzyme systems. *J. D. Fulton.*

ADAMS, A. R. D. & SANDERSON, G. **Studies on Synthetic Antimalarial Drugs. III. A Preliminary Investigation of the Therapeutic Action of 3349 on Acute Attacks of Benign Tertian Malaria.** *Ann. Trop. Med. & Parasit.* 1945, Dec. 31, v. 39, Nos. 3/4, 165–8. **IV. A Preliminary Investigation of the Therapeutic Action of 3349 on Acute Attacks of Malignant Tertian Malaria.** *Ibid.* 169–72. **V. Further Investigation of the Therapeutic Action of 3349 on Benign Tertian and on Malignant Tertian Malaria Infections.** *Ibid.* 173–9, 7 figs. **VI. A Comparison of the Therapeutic Actions of 3349 and of Mepacrine Hydrochloride on Acute Attacks of Benign Tertian Malaria.** *Ibid.* 180–81, 2 figs.

III. In view of the activity of compound 3349 in *P. gallinaceum* infections described above, tests were now carried out in human malaria. The first trials were made on a strain of *P. vivax* which was employed in malaria therapy and had been passaged by blood inoculation. Such infections are easily cured. Five neurological cases were treated orally with 0·2 gm. of 3349 (see Part II) thrice daily on seven consecutive days, while another case received half this amount of drug. The dosage was based on toxicity data for the drug in animals, and it was believed to be not more toxic for mice than mepacrine. In all cases there was a rapid fall in temperature and disappearance of the parasite from the peripheral blood, with no marked evidence of toxicity. Infections with *P. vivax*, in healthy males, which had been acquired in different parts of the world were next treated. These infections were of several weeks' or months' duration and most of the patients had been treated previously with standard antimalarials, or had been given mepacrine prophylactically. All the patients were suffering from clinical malaria and had to be kept in bed. One man was experiencing his first severe clinical attack. Observations were made before treatment was started to verify that the attack was not ending spontaneously. Seventeen acute cases of naturally acquired benign tertian malaria were treated orally with 0·2 gm. of 3349 thrice daily for seven days. A thick blood film of each patient was examined daily while he was in hospital and twice weekly during convalescence. The clinical attack was in each case rapidly terminated by this treatment. Of seven other cases treated with half the dose, three relapsed in 2–3 weeks, three others remained well for 5–8 weeks, while the seventh showed no response to the treatment, but was clinically cured with the larger dose. There were no toxic symptoms with the smaller dose. Further courses of drug were given to some patients to find out if toxic symptoms occurred. One received 0·2 gm. of 3349 thrice daily on two consecutive days each week for 9 weeks, and 15 others 0·1 gm. twice daily for periods up to six weeks. The only untoward symptoms encountered were mild colic and diarrhoea or frontal headache. There was a relapse in one case seven weeks after the first course while receiving 0·2 gm. of 3349 daily.

IV. As the drug 3349 had shown activity in cases of benign tertian malaria, treatment was now begun on cases of malignant tertian infection acquired in W. Africa or in the Mediterranean. Most of the men had been treated previously with standard antimalarials. The duration of the infections was from a few weeks to some months before treatment was begun, but in some patients the first clinical attack of the disease was treated. The authors consider that it has not been clearly shown whether a primary attack of malignant tertian malaria in a patient who has had no prophylactic drug-treatment, or a delayed primary attack in one who has been so treated, is more responsive to chemotherapy than a patient suffering from relapse subsequent to previous courses

of treatment. Their experience leads them to believe that the immediate response to an effective drug is similar in each case. No patients with infection of long standing were included in this study. The conditions for trial were the same as in Part III above. The clinical attack was successfully treated in 25 cases of malignant tertian malaria by 0·2 gm. of 3349 orally thrice daily for seven days. Nine of the patients were then discharged. In five others there was no relapse during a period of 3½ months. Two cases which relapsed in 3–4 weeks were retreated and responded to the above dosage, whereas half the amount of drug proved unsatisfactory in curing clinical attacks or in preventing recrudescence. The remaining nine received a second course of 0·2 gm. of the same drug by mouth daily for 3–6 weeks and remained well and free from parasites during that period. The higher dosage caused slight colic and diarrhoea, and transient headache, in a few instances at the start of the treatment. In 15 cases of the same infection treated orally with 0·1 gm. of the drug thrice daily for seven days, the results were less satisfactory, as the clinical attack was in some cases not arrested, while other patients experienced a rapid recrudescence of the attack. On this dosage there were no untoward symptoms caused by the drug.

V. Further trials with 3349 given orally have now been carried out in 206 cases of benign tertian and in 61 cases of malignant tertian malaria under the same conditions as previously observed. Data have been collected on the relapse rates of patients treated with this drug. Details of the benign tertian cases are dealt with first. Many were treated for "delayed primary attacks" consequent on the discontinuation of prophylactic mepacrine. The effects of different dosage schedules of the drug on the temperature and on the number of asexual forms in the blood are recorded in a number of graphs. Retreatment of relapses was successful and provided no evidence of development of resistance to this drug. Sexual forms of the parasite were unaffected by 3349. The relapse rate in this form of malaria after effective clinical treatment was over 70 per cent. in 126 cases within a period of eight weeks and was fairly constant in the different classes treated. In the case of malignant tertian malaria, 15 acute attacks were treated with 0·1 gm. of 3349 thrice daily for seven days. As in benign tertian, this dosage was unable to control all the attacks and asexual parasites were present in four of the cases on completion of treatment. Double this dose of drug was effective in 32 of 33 cases. Twenty-seven of 28 attacks were successfully treated by 0·5 gm. of the drug given each twelve hours for 2–7 days. Good results were obtained in four patients treated with 1·0 gm. of drug on two occasions with a twelve-hour interval between doses. Relapses were noted under all dosage schedules, except in two cases when 1·0 gm. doses were given. The drug showed no activity against the crescent forms. Only the mild toxic symptoms due to the drug were encountered, as noted in the earlier studies, and they did not prevent continuation of treatment. One patient after a dose of 1·0 gm. of the drug had severe diarrhoea.

VI. When the action of 3349 was being tested on acute attacks of benign tertian malaria, alternate and unselected cases were for a time treated with mepacrine hydrochloride. Both drugs were given orally and their administration was carefully supervised.

Two hundred and thirty-five cases were treated with 3349 in doses regarded as clinically effective, as follows :—

95 cases :	0·2 gm.	of	3349	thrice daily	for	7 days.
28 ,,	0·5 gm.	,,	3349	12-hourly	for	2 days
54 ,,	0·5 gm.	,,	3349	,,	,,	4 ,,
54 ,,	0·5 gm.	,,	3349	,,	,,	7 ,,
4 ,,	1·0 gm.	,,	3349	,,	,,	1 day

For comparison 102 cases received 0·2 gm. mepacrine thrice daily for 2 days and then 0·1 gm. mepacrine thrice daily for 5 days—a dosage previously employed by the authors on an extensive scale in the control of all types of acute malaria infection. The experimental details for each drug are recorded in Figs. A and B in the paper. The following is the authors' comment :—

" A study of Figs. A and B shows very comparable activity of 3349 and of mepacrine hydrochloride in the arrest of acute attacks of *P. vivax* infection. In each series of cases gametocytes were observed to persist in the peripheral blood in about half the cases for periods up to a week after the end of treatment. In neither were the patients unduly inconvenienced by side-effects resulting from the treatment. The absence of yellow staining of the skin in those men treated with 3349 was held by them more than to counterbalance the mild colic or diarrhoea which some of them experienced for the first day or two of this treatment." *J. D. Fulton.*

SPINKS, A. ; TOTTEY, Mary M. **Studies on Synthetic Antimalarial Drugs. VII. Turbidimetric Determination of 2-*p*-Chlorophenylguanidino-4-β-Diethylaminoethylamino-6-Methylpyrimidine (3349)** [SPINKS]. *Ann. Trop. Med. & Parasit.* 1945, Dec. 31, v. 39, Nos. 3/4, 182–9, 4 diagrams. **VIII. Colorimetric Determination of 2-*p*-Chlorophenylguanidino-4-β-Diethylaminoethylamino-6-Methylpyrimidine (3349)** [SPINKS & TOTTEY]. *Ibid.* 190–96, 2 diagrams. **IX. The Excretion of 2-*p*-Chlorophenylguanidino-4-β-Diethylaminoethylamino-6-Methylpyrimidine (3349) in Human Urine** [SPINKS & TOTTEY]. *Ibid.* 197–207, 3 diagrams. [45 refs.]

VII. A turbidimetric method for the estimation of 3349 in biological material has been developed, which is claimed to be simple and accurate. Reference is made to two other methods of estimation and also to a colorimetric method which is described in Part VIII of this series. The present method is accurate to within 10 per cent., and its sensitivity is given as about 2μ gm. of 3349 in any biological material. It is founded on the fact that many basic substances form insoluble salts with complex acids. 3349 was found to give precipitates with a number of organic and inorganic acids and the potassium mercuri-iodide reagent of GENTZKOW [this *Bulletin*, 1938, v. 35, 569] was found to be the most suitable, in that the suspension formed was reasonably stable at high dilution. Precipitation of the base occurs in acid or alkaline solution with this reagent ; it was brought about in N/10 hydrochloric acid since extraction was carried out with this reagent, and results were best as regards opacity of the suspension with that particular concentration of acid. When formed, the suspensions were examined in a direct-reading photoelectric colorimeter, the percentage of light transmitted being in approximate agreement with the galvanometer deflections. The best results were obtained if galvanometer readings were made at 5–10 minutes after formation of the suspension, and the temperature of the reaction or colour of the incident light did not affect the readings to any extent. To obtain the base from the basified biological material continuous extraction with ether was used and the solvent was completely removed before dissolving the base in N/10 HCl. The method can be applied to blood, urine and tissues of animals after administration of large doses of drug ; it is not, however, suitable for human blood or plasma, as the amounts of drug present in these substances are too small, and the colorimetric method of estimation described in Part VIII is then recommended. In the preparation of a standard curve, which could be maintained for permanent reference, the amount of 3349 base present in μ gm. was plotted against deflections of the galvanometer. 2 ml. standards of the base in solution in N/10 HCl containing 0–50 μ gm. in twelve

different tubes were used in its construction and the contents mixed with 0·2 ml. of mercuri-iodide reagent. The deflections were read for each standard 5 minutes after mixing, when the deflection of the blank had been made to read 100 on the galvanometer scale of the colorimeter. [The complete details of the method cannot be given here.]

VIII. A colorimetric method more suitable for the estimation of 3349 in blood and plasma than the turbidimetric method outlined above is described. It depends on the hydrolysis of the substance to *p*-chloroaniline, which is then diazotized and coupled with N-β-sulphatoethyl-*m*-toluidine to give a red dye. As little as 0·4 μ gm. of the drug is estimable in biological material. It was shown by large scale experiment that quantitative hydrolysis of 3349 by N/1 HCl to *p*-chloroaniline did not occur under normal pressure but was achieved by hydrolysis with N/2 HCl under a pressure of 20–25 lb. for 12 hours. In the extraction previous to hydrolysis a mixture of benzene containing 2 per cent. of ethanol gave 100 per cent. recovery of 3349 from biological material by single extraction, after the material had been basified and rendered less viscous by warming at 50°C. for 30 minutes. All the reagents employed were of the highest purity. A standard reference curve was prepared in which μ gm. of 3349 per ml. were plotted against drum readings if the Spekker absorptiometer were used, and against galvanometer deflections in the case of the photo-electric colorimeter. In these determinations, solutions containing 0–20 μ gm. of 3349 per ml. in N/2 HCl were hydrolysed in sealed ampoules under the conditions described above, in volumes of 1½–2 ml. On cooling, 1 ml. aliquots were partially neutralized, diazotized and coupled, and after 10 minutes the yellow colour present was changed to red by 4 drops of concentrated HCl. The volumes were then corrected and readings made on the instrument selected, not more than 1 hour after coupling, while using a filter with maximum transmission at 510 mμ, since the absorption maximum of the coloured substance was at 507·5 mμ.

For estimation in the case of blood, 1–7·5 ml. are used and the blood is laked before being made alkaline. The next steps are as described above. The same principles are employed for estimation in the case of plasma, urine, bile, tissues and faeces. The four last may contain large amounts of drug. [Details are recorded in the paper, but cannot be given here.] Mepacrine in high concentration may interfere with results, and also phenacetin and procaine. Most tissues contain no reacting substances, but blood may give a high blank. The recoveries of drug from blood, plasma, tissues, faeces and urine approached theoretical.

IX. Using the turbidimetric method for the estimation of 3349, the authors measured its urinary excretion in four normal volunteers, each of whom was given 500 mgm. orally twice daily for 4–5 days. Nausea, epigastric pain and diarrhoea occurred, and one subject vomited after the eighth dose. The urine of volunteers was collected regularly for 7 days previous to and for 14 days after treatment started, and irregularly till the amount of drug present was minute. While the drug was being taken, there was a diminution in urinary output, probably as the result of diarrhoea, but there was neither glycosuria nor albuminuria. The percentage of the daily intake of drug excreted in the urine continued to increase while the doses were maintained but it was not constant by the fifth day, when dosage ceased. After that time there was a rapid fall in output. Minute amounts of drug were still present in the urine 23 days after the start of treatment, which suggested that it was being retained in the tissues. About 4 per cent. of the total drug administered was found in the urine of each volunteer, and likewise in that of treated rabbits and rats. In its manner of excretion 3349, therefore, resembles mepacrine. Since it was shown in Part VII that *p*-chloroaniline was a hydrolytic product of 3349

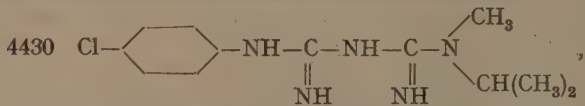
and possibly acetone as well, the excretion of aromatic amine, of total amine, and of acetone was measured during the experiment. Paradoxically, the amount of " total " amine found was less than that of " free " amine, possibly due to the presence of esters of aminophenols. There was a significant increase in excretion of aromatic amine while the drug was being taken, but it represented only a very small conversion of 3349 to *p*-chloroaniline. There was no evidence that 3349 gave rise to acetone in the human subject. It is well known that many aromatic substances are converted in the body to hydroxyl derivatives which are then excreted as aryl sulphates or glucuronides. Measurements of the amount of these substances excreted were made while looking for a clue to the method of detoxication of 3349, but none was obtained. A search for metabolites of 3349 was also made in urine, but only the parent substance was isolated. By quantitative experiments in the isolation of added 3349 from urine, it was shown that the substance estimated as 3349 by the turbidimetric method of Part VII was indeed that substance possibly contaminated with very small amounts of basic metabolites, as judged by ultraviolet absorption spectra. Work in progress suggests that most of the 96 per cent. of administered 3349 still unaccounted for may be present in faeces. The possibility of formation of a hydroxyl derivative of the parent substance, the deamination of the latter, or alteration in the side-chain is, however, not excluded. *J. D. Fulton.*

CURD, F. H. S., DAVEY, D. G. & ROSE, F. L. **Studies on Synthetic Antimalarial Drugs. X. Some Biguanide Derivatives as New Types of Antimalarial Substances with both Therapeutic and Causal Prophylactic Activity.** *Ann. Trop. Med. & Parasit.* 1945, Dec. 31, v. 39, Nos. 3/4, 208–16. [10 refs.]

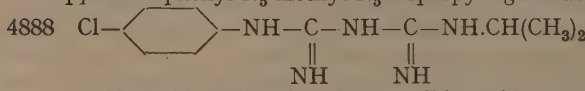
ADAMS, A. R. D., TOWNSHEND, R. H. & KING, J. D. **XI. An Investigation of the Therapeutic Action of 4430 on Benign and Malignant Tertian Malaria.** *Ibid.* 217–19.

SPINKS, A. & TOTTEY, Mary M. **XII. Determination of N_1-*p*-Chlorophenyl-N_5-Methyl-N_5-Isopropylbiguanide (4430) and N_1-*p*-Chlorophenyl-N_5-Isopropylbiguanide (Paludrine) : a Preliminary Report.** *Ibid.* 220–24, 1 diagram.

X. In this paper a preliminary account is given of the chemical considerations leading to the synthesis of biguanides with marked action on the blood and exoerythrocytic forms of certain avian malaria parasites. The chemical constitutions of two of these substances are as follows :—



N_1-*p*-chlorophenyl-N_5-methyl-N_5-isopropylbiguanide acetate



N_1-*p*-chlorophenyl-N_5-isopropylbiguanide acetate

Both are colourless, crystalline substances soluble in water. The action of the former is analogous to that of certain sulphonamides in avian malaria, whereas the latter has some unique properties in this infection which suggest that an advance has been made in the prevention and treatment of malaria. While 4430 is a causal prophylactic against *P. gallinaceum* only and is ineffective against the blood forms of *P. cathemerium*, 4888 acts both as causal

prophylactic and as a therapeutic agent in the four types of avian malaria studied. The probable life-cycle of the malaria parasite in the vertebrate host as outlined by a number of workers including Huff *et al.* [this *Bulletin*, 1943, v. 40, 815; 1945, v. 42, 538] and Davey [this *Bulletin*, 1944, v. 41, 365] leads the authors to believe that drugs with an action against exo-erythrocytic forms are of paramount importance, and that on this action causal prophylaxis and prevention of relapses probably depend. James, especially, has long put forward similar views, although the presence of such forms has not yet been satisfactorily demonstrated in human malaria. After the synthesis of certain pyrimidine derivatives described in Parts I and II of this series, which contained an —NH—(imino group) or HN—C—NH (guanidino group) between the

ring systems, theoretical considerations led the authors to the synthesis of compounds with a new linkage—HN—C—NH—C—N=(biguanidino group). The

substitution of other heterocyclic ring-systems than pyrimidine opened further possibilities, but the authors stress the practical need for simplicity of synthesis and the retention only of groups necessary for antimalarial activity. It was found that the pyrimidine ring was not essential. Biguanides are easily synthesized, and in this reaction ammonia or an amine takes part. The first member of the new series proved inactive in *P. gallinaceum* infection, on account, it was believed, of its too strongly basic character. By selecting suitable amines for the reaction the active substances 4430 and 4888 were obtained. [The latest views of the authors on these matters have recently been given to the Chemical Society.]

In the case of *P. gallinaceum* and *P. relictum*, sporozoites have been shown to undergo a cycle of development in tissues, and have been designated by the authors as primary exoerythrocytic (e.e.) forms. A causal prophylactic drug would act against either of these forms. No drugs are yet known which act against sporozoites but the properties especially of 4888 suggest that it may act as a causal prophylactic in human malaria. When the development of primary e.e. forms is completed, the blood is then invaded, and during multiplication in the latter site there is a concomitant increase in tissue forms. From the reaction of the tissue forms to drugs, they appear to differ from primary e.e. forms; they have been designated secondary e.e. forms, and may be derived from blood forms, as they can be transmitted by blood inoculation. Since a radical cure of avian malaria is not easily obtained, in which respect it resembles benign tertian malaria, the presence of secondary e.e. forms, in the latter infection, although not yet demonstrated, may be the explanation of the failure to effect cure. The search for a drug active against the blood forms of human malaria, but without the practical drawbacks of mepacrine both as regards dyeing properties and the many steps in its synthesis, has not been neglected. A comparison of the action of 4430 and 4888 as causal prophylactics and in treatment of blood infections has been made with that of quinine, mepacrine, and sulphonamides in four species of avian malaria, and the results are given in a table. The properties of the two new drugs were such as to justify their trial in human malaria.

XI. This note records the first trials in human malaria of the new drug 4430 described in Part X. The early dosages ranged from 20–500 mgm. orally, thrice daily, without evidence of serious effects. When 1 gm. doses were given, more or less severe toxic symptoms were encountered. Benign and malignant tertian malaria naturally acquired was treated in healthy subjects after their return from service overseas. Most of them had taken mepacrine

or quinine prophylactically, and there was in some cases a history of previous clinical attacks. The conditions of treatment were the same as those described in Part III and subsequent papers of this series. In 44 cases of benign tertian malaria the clinical attack was rapidly cured with all the dosages of drug employed. Temperature became normal within 72 hours and the peripheral blood was freed from parasites within 96 hours after the start of treatment but gametocytes were present after 6 days. The details of these cases are recorded in tabular form. More than half the cases relapsed independently of the dosage given. In nine cases of naturally acquired *P. falciparum* infection similar results were obtained. The crescent forms appeared to be unaffected by the drug. One-third of the cases were known to have relapsed with different dosages, but in two receiving the highest dosage given for 1 week, no relapse occurred. Doses of 1 gm. or more of the drug daily caused nausea and vomiting. The highest doses gave rise to loin-pains, vomiting, sweating, oliguria, albuminuria and haematuria or the presence of red cells in the urine. With copious fluids, recovery was complete in 24 hours. In subsequent cases, a liberal fluid intake when the drug was being administered avoided renal complications.

XII. This is a preliminary report on the estimation of the two drugs 4430 and 4888 (Paludrine) described in Part X of this series. On account of the presence of a *p*-chlorophenylguanidine residue which can be hydrolysed to *p*-chloroaniline, apparently more readily than in 3349, the same colorimetric method of estimation can be employed as for the latter substance. The two newer drugs are recoverable quantitatively from blood, plasma, and tissues with the same method of extraction. In their case N/4 HCl is used for both extraction and hydrolysis, and partial neutralization becomes unnecessary. Details of the method are given for blood, and it can be adapted to other biological materials. As before, it consists essentially in laking, basifying, rendering less viscous by heat, and then extracting the base with benzene-ethanol. An aliquot is then hydrolysed under pressure in a sealed ampoule with N/4 HCl, followed by diazotization and coupling to give a coloured substance which is estimated in a photoelectric colorimeter, not more than one hour later, and compared with a standard curve compiled from known amounts of material. On account of lower molecular weights of 4430 and 4888 smaller amounts can be estimated than in the case of 3349 and the levels of the former are actually higher in blood, plasma and urine but not in faeces and tissues. The amounts estimable depend on the apparatus available. Some instruments allow 0·2 μ gm. in aqueous solution to be estimated, but the sensitivity of the method can be increased 3–5 times by special apparatus. Purity of reagents and cleanliness of apparatus are vital for success with these small amounts, and frequent blank determinations should be used as check. Recovery from plasma and urine approached the theoretical, while the accuracy was somewhat lower in the case of blood and tissues. *J. D. Fulton.*

ADAMS, A. R. D., MAEGRAITH, B. G., KING, J. D., TOWNSHEND, R. H., DAVEY, T. H. & HAVARD, R. E. **Studies on Synthetic Antimalarial Drugs. XIII. Results of a Preliminary Investigation of the Therapeutic Action of 4838 (Paludrine) on Acute Attacks of Benign Tertian Malaria.** *Ann. Trop. Med. & Parasit.* 1945, Dec. 31, v. 39, Nos. 3/4, 225–31, 4 figs.

MAEGRAITH, B. G., ADAMS, A. R. D., KING, J. D., TOWNSHEND, R. H., DAVEY, T. H. & HAVARD, R. E. **XIV. Results of a Preliminary Investigation of the Therapeutic Action of 4888 (Paludrine) on Acute Attacks of Malignant Tertian Malaria.** *Ibid.* 232–6, 1 fig.

XIII. This preliminary report describes the first clinical trials with "Paludrine" (4888) given orally in acute attacks of benign tertian malaria. The

tests were initiated when it was found that the drug was probably curative in *P. gallinaceum* infections of chickens. The patients were Service men suffering from primary attacks of benign tertian malaria or from relapses. No patient in whom the clinical attack had lasted more than one week was included in the series. Suppressive mepacrine had been taken by most, and some had been treated with the standard antimalarials, in all cases more than two weeks before hospitalization. The same conditions of treatment were observed as described in Part III, etc., of this series. Experimental data in animals suggested that 40 mgm. per day would be a safe dose in man, and 20 mgm. were therefore given 12 hourly on 14 consecutive days, a treatment which proved clinically effective. The dosage was increased step-wise to 700 mgm. twelve hourly in later cases, and careful watch was kept on the patients for any untoward symptoms. Doses of 10 mgm. 12-hourly were successfully employed in three cases but below this level clinical results were variable. Blood films were examined twice daily till parasites disappeared, and thereafter daily while the patient was under observation. The detailed results of treatment of 147 cases with doses ranging from 10 to 700 mgm. 12-hourly for 14 or 28 days are recorded graphically along with those for 188 similar cases treated with mepacrine in doses of 0·8 gm. daily for two days followed by 0·3 gm. daily for 10 days. " Paludrine " controlled the acute attacks, over the range studied, as effectively as mepacrine. Toxic symptoms seen in a few cases included vomiting and epigastric pain, but it was never found necessary to interrupt treatment, and regular urine examinations disclosed no abnormality. Estimations of drug concentration in whole blood, plasma and urine have been made following single doses of 50 and 500 mgm. In whole blood the estimations were unreliable, as previously observed for mepacrine, and were therefore abandoned. The plasma and urinary concentrations after the standard therapeutic dosage with 50 or 500 mgm. 12-hourly for 14 days were also determined. In these cases the plasma concentration rose rapidly, and remained fairly steady from the fourth to fifth day of treatment. When treatment ended there was a rapid fall in the concentration. The urinary output followed a similar pattern, and in urine the drug was detectable in some cases for nine days after the end of treatment. The fall in plasma-level and in urinary output are more rapid than in the case of mepacrine.

XIV. The treatment of 22 cases of recently acquired malignant tertian malaria with Paludrine (4888) orally is reported in this note. Sixteen of the patients had no previous history of malaria, the others had had one previous attack of malignant tertian malaria. Seven had received no suppressive treatment, while the remainder had taken quinine or mepacrine. No antimalarial treatment had been given for at least two weeks before treatment with " Paludrine " was begun. All the subjects were kept in bed, and the conditions of treatment as outlined in Part III were observed, except that in some cases the patients were ill on admission and treatment was started within 24 hours. The first dosage schedule tried was 50 mgm. 12-hourly for 14 days, and during treatment the patient was encouraged to drink plenty of fluids. The clinical attack was controlled in all cases with the above dosage. Later cases were given 200, 500 or 600 mgm. doses in the same way. Therapeutic results were judged as in previous trials. With this treatment, asexual parasites rapidly disappeared from the peripheral blood, temperature was controlled, and the condition of the patient rapidly improved. Gametocytes were unaffected. The clinical results obtained so far are comparable with those in benign tertian malaria. A few patients vomited after the drug but probably not on account of it, as vomiting ceased with improvement of the clinical condition. There were no other untoward effects. *J. D. Fulton.*

KELSEY, F. E., OLDHAM, F. K. & GEILING, E. M. K. **Studies on Antimalarial Drugs. The Metabolism of Quinine and Quinidine in Birds and Mammals.** *J. Pharm. & Exper. Therap.* 1945, Oct., v. 85, No. 2, 170–75, 1 fig.

In previous papers Kelsey and Oldham [this *Bulletin*, 1944, v. 41, 260] have investigated the ability of tissues of different species of animals to metabolize quinine *in vitro* and have suggested that there is a probable relationship between *in vitro* and *in vivo* metabolism. In a similar way *in vitro* studies have now been made on the metabolism of quinidine—the optical isomer of quinine—by tissues of various birds, rats and rabbits. Tissues were homogenized in a Waring Blendor in Ringer-Locke solution and filtered through gauze. Aliquots representing different weights of tissue were mixed with 0·1 mgm. of the two alkaloids in 10 cc. Ringer-Locke solution, which was used to make the total volume up to 20 cc. After incubation for 6 hours at 38–40°C. the percentage degradation of these substances was estimated by a method previously employed by the authors. In the *in vivo* studies, adult rabbits, chickens and ducks were given 10 mgm. of the alkaloids per kilogram intravenously, and were sacrificed 10 minutes, 1 hour and 4 hours after injection of the drug. Post-mortem degradation in the weighed tissues was prevented by 2 per cent. NaOH. *In vitro* it was found that quinine was more readily metabolized than quinidine by rat and rabbit tissues, while the converse was true when tissues from various birds were used. The rabbit metabolized quinine more rapidly than quinidine *in vivo*, whereas in the duck and chicken both appeared to be metabolized at similar rates, the rate in the duck being slower than in the chicken. Papers by KELSEY *et al.* [this *Bulletin*, 1944, v. 41, 11], WALETZKY & BROWN [*ibid.*, 1944, v. 41, 188] and by HIATT & QUINN [*ibid.*, 1945, v. 42, 778] are of interest in this connexion. The distribution of these alkaloids between red cells and plasma in the case of ducks and chickens was found to be different. These experiments show that the fate of the two drugs in the chicken and duck is not identical and the results of antimalarial tests in the two species may thus be different. *J. D. Fulton.*

DEARBORN, E. H. & MARSHALL, E. K., Jr. **The Degradation of Quinine in the Duck, Chicken and Dog.** *J. Pharm. & Exper. Therap.* 1945, Oct., v. 85, No. 2, 202–5. [12 refs.]

Different methods for the estimation of quinine in the blood and tissues of animals have been described [this *Bulletin*, 1944, v. 41, 11, 188, 260 ; 1945, v. 42, 778]. In some of these cases the method of assay has included degradation products of the alkaloid. In the present investigation, quinine was administered to ducks and chicks by the drug-diet method of MARSHALL *et al.* [this *Bulletin*, 1943, v. 40, 223] or intravenously and by the latter method to dogs. By the use of selected methods devised by BRODIE and UDENFRIEND for the estimation, the evidence obtained suggests that more than one degradation product of the alkaloid was formed. By the first method [this *Bulletin*, 1943, v. 40, 821] total acid-soluble fluorescence is estimated ; by the second, fluorescence after alkaline extraction ; and in the third, which proved most reliable for the estimation in plasma, the base is made to combine with methyl orange after alkaline extraction (*J. Biol. Chem.*, 1945, v. 158, 705). The quenching of fluorescence by salt in the first method suggested that only traces of the degradation product described by KELSEY *et al.* [this *Bulletin*, 1944, v. 41, 923] were present, and this was supported by other evidence. The concentration of " quinine " in the plasma of ducks, chicks and dogs was estimated by each method, and also that in the liver of chicks and ducks. By the use of what was termed " quinine oxidase " of rabbit liver by KELSEY and OLDHAM [this

Bulletin, 1944, v. 41, 260], which converts quinine to a 2-hydroxy derivative as shown by MEAD and KOEPFLI [this *Bulletin*, 1945, v. 42, 9], successful degradation of quinine was accomplished in duck plasma, but only to a limited extent in plasma of chicks or dogs.

From the results obtained by the three different methods of estimating "quinine" the authors conclude that :—

"(1) There are probably at least two degradation products of quinine to be found in the duck after administration of quinine.

"(2) The degradation of quinine appears to be qualitatively similar in ducks, chicks and dogs." *J. D. Fulton.*

MERGENER, J. C. **Psychosis following Administration of Quinacrine Hydrochloride for Malaria. Neuropsychiatric Study of a Case.** *War Medicine.* Chicago. 1945, Oct., v. 8, No. 4, 250–52.

A soldier, 25 years of age, suffered from a primary *P. falciparum* infection and was treated with quinacrine (mepacrine). During a period of five days he received 2·8 gm. On the fifth day signs of mild excitement appeared ; he became very talkative ; his speech was rambling and at times disconnected, and it was impossible to keep him in bed. A sedative was given ; quinacrine was stopped. The excitement increased the next day ; euphoria and hyperactivity necessitated his being placed in a locked ward. The hyperactivity gradually gave way to a confusional state which bordered on depression ; he became disoriented for time, place and person. His replies to questions became slow and reflected inner confusion. A possibility that cerebral malaria might be the cause of the psychosis prompted the administration of quinine. For six days his condition changed but little ; then gradual improvement began. In all, the mental disturbances lasted 14 days before recovery was complete. When he was discharged from hospital, a fine tremor of the hands persisted. Several interviews after his recovery failed to reveal anything psychiatrically abnormal, and there was no antecedent history of psychiatric factors which might have predisposed to the onset of mental symptoms. No recurrence of the symptoms had been noted three months after recovery. [See also this *Bulletin*, 1945, v. 42, 9 ; 1946, v. 43, 297.] *Norman White.*

ZYLMANN, G. In vitro—und in vivo—Versuche über die hämolytischen Eigenschaften der synthetischen Malariamittel. [*In vitro* **and** *in vivo* **Experiments on the Haemolytic Properties of Synthetic Remedies for Malaria.**] *Deut. Tropenmed. Ztschr.* 1944, Jan. 1, v. 48, Nos. 1/2, 7–18. [15 refs.]

This paper contains a brief review of the German literature on the subject. The *in vitro* experiments were designed to compare the lytic action in human cells (from normal persons and patients with M.T. and B.T. malaria) of "equivalent," serially diluted solutions of quinine, atebrin, plasmoquine and a "Präparat x."

Quinine had a lytic effect on all red cells over a range of concentration of 1/50 to 1/800 molar. Atebrin lysed normal red cells over a range of concentration of 1/50 to 1/200 molar ; it lysed cells from both B.T. and M.T. patients at dilutions of up to 1/400 molar. The author concludes that the haemolytic effect of atebrin is more pronounced on cells from malaria patients than on those from normal subjects. (Three normal persons, three M.T. cases and eleven B.T. cases were examined.) Plasmoquine had little effect, except for a "very slight" lytic action in the middle range of concentrations. "Präparat x" had no lytic action. The author attempted to repeat, with atebrin, NOCHT and KIKUTH's experiments with quinine [this *Bulletin*, 1929, v. 26, 1028]. Atebrin by itself had

no lytic effect ; amboceptor gave rise to haemoglobinaemia in one animal, and haemoglobinuria in two (out of four). Amboceptor and atebrin injected together gave rise to haemoglobinaemia in three, and haemoglobinuria in two animals (out of four). The author considers that this results indicate that atebrin has a strengthening effect on the haemolytic action of the amboceptor. He points out that more *in vivo* experiments are required to substantiate this. [No account of the composition of " Präparat x " is given, presumably because the paper was published during the war.] *B. G. Maegraith.*

Mohr, W. Atebrin-Ueberempfindlichkeit. [**Hypersensitivity to Atebrin.**] *Deut. Tropenmed. Ztschr.* 1944, Apr.–May, v. 48, Nos. 7/10, 177–82.

The author reviews the available literature on atebrin sensitivity and notes that with the usual dosage régimes, evidence of true sensitivity is very rare. Atebrin poisoning is not common even after high dosages. In the literature reviewed, which includes an account of malaria in German troops in the recent war, only three cases of " idiosyncratic allergic " reactions to atebrin are described.

The author describes a case in which the patient developed a resistant urticaria after atebrin administration for the treatment of malaria (species of parasite not determined, but thought to be *Plasmodium falciparum*). Skin tests showed this patient to be sensitive to atebrin, but not specifically ; he was also sensitive to quinine (to a lesser degree) and to a variety of food substances, including meat and mushrooms. *B. G. Maegraith.*

Yudkin, J. **Non-Absorption of Mepacrine : Description of a Case.** *Brit. Med. J* 1946, Feb. 23, 271, 1 chart.

" A case of M.T. malaria in a European in West Africa which failed to respond to intensive therapy with oral mepacrine is described. Urinary analysis showed that the patient was not absorbing the drug. Subsequent administration of mepacrine intramuscularly resulted in a rapid recovery."

Breslow, D. S., Walker, H. G., Yost, R. S., Shivers, J. C. & Hauser, C. R. **Synthesis of Antimalarials. IV. The Synthesis of certain Compounds related to Quinacrine.** *J. Amer. Chem. Soc.* 1946, Jan., v. 68, No. 1, 100–102. [Refs. in footnotes.]

Bercovitz, Z. T. **Malaria complicated by Pneumonia ; Treatment with Sulfadiazine and Atabrine.** *Ann. Intern. Med.* 1945, July, v. 23, No. 1, 79–82.

This is a case report of a patient who suffered concurrently from *P. falciparum* malaria and lobar pneumonia, type 7 pneumococcus. The administration of atabrine did not in any way influence the effect of sulphadiazine on the pneumonia. The patient received 59·5 gm. of sulphadiazine over a period of 12 days. Atabrine 0·1 gm. daily was given for 22 days while he was under treatment for pneumonia, and for 60 days on two occasions subsequently, without harmful effect. Reference is also made to another similar case in which atabrine and sulphathiazole were used with success. *Norman White.*

Coxon, R. V. & Hayes, W. **Investigation into the Efficacy of Sulphadiazine in the Treatment of Malaria.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1945, Dec., v. 39, No. 3, 195–205, 2 graphs.

Twenty cases of malaria, including fresh and relapsing cases of benign tertian and of malignant tertian, and one quartan infection, were treated with

sulphadiazine. Ten cases receiving only non-specific symptomatic treatment served as controls. Comparison was also made with results achieved by quinine-atebrin-plasmoquine treatment. The dosage of sulphadiazine in most cases was a loading dose of 5 gm. in the first 4 hours, followed by 1 gm. 4-hourly [apparently for 12 days]. With this dosage the concentration in the blood remained at approximately 10 mgm. per 100 cc. throughout the course.

For the enumeration of parasites an absolute method of counting was used : oxalated blood was drawn up to the 20 cmm. mark of a Sahli haemoglobinometer pipette and then discharged on a slide and spread accurately and evenly over an area of 2 sq. cm. The film was allowed to dry on a level surface, dehaemoglobinized with distilled water and stained by Field's stain. Before a sample of blood was reported negative at least 100 fields, representing 0·5 cmm. blood, were examined. The advantage of this thick film method over the thin was shown in the first twelve cases treated with sulphadiazine ; the average day after the beginning of treatment on which the blood first failed to show parasites was 3·7 by the thin, and 8 days by the thick, film method.

The average duration of fever after commencement of treatment with sulphadiazine was 4½ days in *P. vivax* infections, 6 days in *P. falciparum* infections. Of the untreated controls, four spontaneously lost their fever within 12 days of onset ; in the remaining six the fever was virtually unaltered in degree at the conclusion of the 12th day.

The average time for the blood to become parasite-free (asexual forms) after the beginning of treatment was 8 days for both *P. vivax* and *P. falciparum* infections. This does not refer to gametocytes. None of the untreated controls was free from parasites within the 12-day period of observation. In nearly all sulphadiazine-treated patients the parasite count began to fall soon after the commencement of treatment, and steadily declined to zero. In only one case did the parasites appear to be resistant to the drug. With quinine there was a complete clearing of the blood within 5 days. Gametocytes appeared to be completely unaffected by sulphadiazine. Several patients were given higher doses than the standard, *viz.* a maintenance dose of 2 gm. 4 hourly, thus securing blood levels of 17–20 mgm. per 100 cc. The response was not materially different from that obtained by the standard dose.

Of the 20 cases treated with sulphadiazine, 15 relapsed within one month from the end of treatment. Fifteen cases that had received standard army treatment—quinine 4 gm., atebrin 1·5 gm. and plasmoquine 0·15 gm. over a period of 14 days—only one relapsed during a period of one month.

The only complications of treatment, apart from vomiting in a few patients, were renal. Four patients had renal colic ; two of these had haematuria, but no crystals of the drug were found in the urine. In no case was there a dangerously low white blood cell count.

Sulphadiazine has definite antimalarial properties, but the action is inferior to and slower than that of either quinine or atebrin, and treatment with it is followed by a much higher relapse rate.

The inquiry revealed that the corrected erythrocyte sedimentation rate is of no value in assessing the probability of relapse after treatment in malaria.

Norman White.

STEVENSON, D. S. **The Use of Calcium Gluconate in the Treatment of Malarial Chills.** *Puerto Rico J. Pub. Health & Trop. Med.* 1944, June, v. 19, No. 4, 602–13, 2 figs. [20 refs.] [Spanish version 614–25.]

The most distressing symptom of malaria is the chill that usually precedes the fever. These chills may last from a few minutes to over three hours. The author reports the results of treatment of malarial chills.

As soon as possible after onset of the chill, 10 cc. of a 10 per cent. solution of calcium gluconate is given intravenously, very slowly. Fifty trials were carried out on 40 patients and the results are tabulated. In only 2 trials did calcium fail to have an observable effect, and in both these the chill had lasted some time before treatment was given. All cases treated within 5 minutes of the onset of the chill showed complete relief within an average time of 3·7 minutes after injection; if the injection was delayed more than 5 minutes after the onset of the chill, the chill had an average duration of 9·7 minutes. In some cases relief is almost instantaneous. Most of the cases treated were *P. vivax* infections: there were, however, 5 *P. falciparum* and 4 mixed infections. All responded equally well.

In the 50 trials 14 patients complained of untoward effects: nausea and vomiting 4; headache 6; oppression over the chest 1; epigastric discomfort 1; flushing of the face 1; dizziness 1. None of these symptoms was severe enough to suggest that calcium gluconate should not have been given.

The precautions recommended are: careful venipuncture to avoid extravasation of calcium solution into subcutaneous tissue, which might cause necrosis; slow injection; the patient should be recumbent for 15 minutes after the injection; intravenous calcium is contraindicated in cardiac cases, particularly those with arrythmias and bradycardia and in patients receiving digitalis therapy. *Norman White.*

Mohr, W. Zur Behandlung der Malaria tertiana mit intravenösen Gaben von *Tartarus stibiatus.* [**The Treatment of Benign Tertian Malaria by Intravenous Doses of Antimony Tartrate.**] *Deut. Tropenmed. Ztschr.* 1944, Apr.–May, v. 48, Nos. 7/10, 169–76, 2 figs. [18 refs.]

The author reports the use of intravenous antimony tartrate in four cases of inoculated benign tertian malaria. This treatment has no advantage over atebrin in the acute malarial attack but may be indicated in relapses occurring very soon after "curative" treatment. Combined therapy may assist erythropoiesis. The X-ray shadows of both spleen and liver are intensified under antimony treatment. *B. G. Maegraith.*

Bratton, A. C., Jr. **A Short-Term Chronic Toxicity Test employing Mice.** *J. Pharm. & Exper. Therap.* 1945, Oct., v. 85, No. 2, 111–18, 3 figs.

In the preliminary testing of antimalarials it was necessary to carry out chronic toxicity determinations on the more active new substances. For this purpose the drugs were incorporated in the diet of mice, and to meet possible criticisms of this method it was shown by experiment that the results differed in no essential respects from those obtained through giving the drugs by stomach tube. The mouse has certain advantages over the rat as an experimental animal, in that drug-diets can be quantitatively administered, less drug is required per animal, and the intake of the mouse is, in general, more satisfactory. In this communication, the method of administering drug-diets to groups of 10 mice for a period of 7 days is described. Valuable information was obtained by this means regarding the toxicity of these substances in man. A simple type of cage with feeding arrangements was used, in which each animal was housed individually. Sufficient diet was prepared for each group of mice, using starch as excipient for the drug, before incorporation with the main diet in different concentrations. Mice weighing around 16 gm. were found most satisfactory,

and in practice the total weight of a group was used for assessment of results. The animals, not excessively hungry when the experiment started, were kept on a schedule of light and dark, 3 hours of each alternately, and the drug was therefore administered in a manner resembling that employed in human malaria, where several daily doses are usually given. The amount of diet consumed, day of death and other relevant data were recorded. Many factors had to be considered in interpreting the results. Death of the animal proved the most reliable guide in evaluating the toxicity of large numbers of compounds. The mean daily drug intake which allowed the survival of 9 out of 10 mice over the experimental period was selected as the objective. Many data were collected on weight-loss under different régimes of diet and they generally indicated a different value for toxicity from that based on death as the end-point. In each experiment a suitable compound was chosen as a reference standard for toxicity. The value of the method may be judged by the fact that quinacrine [mepacrine] hydrochloride was found to be four times as toxic and pamaquin hydriodide 14 times as toxic as quinine hydrochloride.

J. D. Fulton.

RIBBANDS, C. R. **The Use of DDT as a Mosquito Larvicide on Still Waters.** *Bull. Entom. Res.* 1945, Nov., v. 36, Pt. 3, 315–30.

The effect of DDT, both in oil solution and as a dust, was tried in a number of artificial breeding pits, 4 ft. × 3 ft., filled naturally with seepage water and containing larvae of *Anopheles culicifacies, A. vagus, A. barbirostris* with a few *A. hyrcanus* and *A. subpictus*. Preliminary control trials showed that oil itself at a dose of 4 pints per acre had no deleterious effect on larvae, and twice this amount produced a reduction which was not necessarily significant. Five per cent. DDT in oil at doses of one-third and one-half pint per acre caused 90 per cent. mortality of anopheline larvae, and doses over one pint consistently caused 100 per cent. mortality in 24 hours. Malariol, kerosene, and waste engine oil were used as solvents and it was found that the vehicle made no appreciable difference to the efficiency of the DDT. It does not kill eggs, hence young larvae may hatch out soon after treatment with heavy doses, a fact which may obscure the residual action if all larvae are counted, a better guide to effectiveness being the presence of 2nd to 4th instar larvae. Using this as a criterion, doses of 2 gallons of 5 per cent. solution per acre give complete control for 11 days, 30 per cent., control up to the 18th day, and some degree of control up to a month, whereas oil itself is completely ineffective by the eleventh day.

A series of trials was made in natural waters with the object of determining the average distance through which small quantities of DDT in waste engine oil would spread and exert a lethal effect when applied at a single point. Small quantities of oil solutions were applied by means of a pipette at the edge of breeding places and the extent of the perimeter sterilized of larvae was measured, some of the results being summarized below.

From these results it is concluded that DDT solutions are lethal in the stable and far-reaching monomolecular films, which are the final end of all oil solutions on a water surface. The application of these conclusions was checked by controlling breeding in a marsh by the distribution of DDT oil solution cast on in 5 cc. doses at intervals of 12 ft. around the perimeter; the use of very simple apparatus is recommended. [These observations on the spread of DDT solutions are of considerable practical value, for they indicate that there is no need for spraying apparatus more complicated than an oil-can or a drop bottle. It is unfortunate that the use of a trade-name, the " RKW oil squirt," lends complication to a paper which otherwise goes far to simplify technique.]

TABLE X.

Distance of Complete Anopheline Kill.

Expt.	Type of Pond	Weather	Distance of Complete Anopheline Kill, in feet				
			¼ cc.	1 cc.	2 cc.	4 cc.	8 cc.
1	Open Water ...	3 hours Rain	—	10	23	—	40
2	Weedy Pond ...	2½ ,, ,,	15	—	—	—	—
2	,, ,, ...	,, ,, ,,	7	7	—	29	63
3	,, ,, ...	Fine	—	28	—	59	—
4	,, ,, ...	,,	—	41	65	70	100
4	,, ,, ...	½ hour Heavy, and 2 hours Light Rain	—	32	40	67	67
5	*Pistia* covered Pond	Fine	12	7	—	25	—
5	,, ,, ,,	2½ hours Rain	15	10	—	27	—
5	,, ,, ,,	,, ,, ,,	—	10	—	—	—
5	,, ,, ,,	2 ,, ,,	13+	20	—	29	—
5	,, ,, ,,	,, ,, ,,	—	20	—	—	—
	Minimum Length of Kill		7	7	23	25	40
	Average Length of Kill		12	19	42	44	67

G. Macdonald.

DEONIER, C. C. & BURRELL, R. W. **Airplane Application of DDT Larvicides.** *J. Econom. Entom.* 1945, Aug., v. 38, No. 4, 425–7.

The application of DDT as a dust from aircraft presents several technical difficulties, and is not a certain means of killing mosquito larvae. The application of solutions, or emulsions, by this means, however, is a very promising method of mosquito control. Less weight of material need be carried than when paris green is being applied, the droplet size can be regulated, low flying is not necessary, and the method is convenient. Preliminary tests gave kills varying from 94·9 per cent. to 100 per cent. in vegetated marshes, and 100 per cent. in open water. Further studies are in progress. *G. Macdonald.*

HAWKING, F. **Growth of Protozoa in Tissue Culture. I.** ***Plasmodium gallinaceum*, Exoerythrocytic Forms.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1945, Dec., v. 39, No. 3, 245–63, 29 figs. [12 refs.]

The paper describes the author's attempts to cultivate *Plasmodium gallinaceum in vitro*. He had little success with the erythrocytic stages. The utmost was a survival of parasites for five days, as proved by injection of clean chicks. The inoculation of chick embryos was carried out by various methods on 69 eggs. In most cases the embryos died, but on 14 occasions chicks hatched. In no case were malarial parasites present in the blood at the time of hatching, but in three they appeared in 10 to 14 days. As noted by the author in his preliminary paper [this *Bulletin*, 1944, v. 41, 732] striking results were obtained with exoerythrocytic stages grown in cultures of macrophages and related cells. The tissue cultures were set up in Carrel flasks, to the bottom of which four to six cover glasses were fixed by means of fowl plasma. On each cover glass a drop of plasma is placed and a small portion of the tissue to be cultivated, usually the spleen, is introduced into this plasma by means of a pipette, which also serves

for the removal of excess of plasma. When the plasma has coagulated and the embedded tissue is fixed to the cover glass, the fluid medium (Tyrode's solution) is added. The cultures are incubated at 37°C.

When the cultures were started from the tissues of chicks previously inoculated with sporozoites of *P. gallinaceum*, developmental forms of this parasite appeared in the macrophages and other cells. These were detected by removing one of the cover glasses and examining it microscopically after fixing and staining the growing cells and parasites on its surface. Positive cultures have been obtained from the spleen, bone marrow, buffy coat of centrifuged blood, and liver. In spite of its heavy content of exoerythrocytic forms, the brain failed to yield a positive culture. In any positive culture, parasites in all stages of development are present at the same time—forms with one, two, four and more nuclei (up to 50 or more) within the cytoplasm of the cells. Extracellularly, merozoites may be detected. These have a central nucleus, and are rounded at one end and pointed at the other. Toward the rounded end a granule of volutin is often present. Usually the cultures were made from the tissues of the chicks 7 or 8 days after the inoculation of sporozoites. Positive cultures have, however, been made before this, the earliest being one hour after the inoculation of sporozoites. In some instances tissue cultures started from the spleen of an uninfected chick have been infected by introducing parasites from a positive culture, but attempts at further passage were not successful. The viability of the parasites in cultures was tested by inoculation of chicks. The oldest culture which proved infective was one at its 89th day. Microscopically parasites were detected in cultures up to 61 days, but with increasing age more degenerating cells and parasites occur. Attempts to commence cultures by introducing sporozoites into tissue cultures were not successful nor was it possible to infect erythrocytes by introducing these to cultures. In general, the development of *P. gallinaceum* in cultures corresponds very closely with the course of development of the parasite in chicks following sporozoite inoculation. The paper is illustrated by photomicrographs and by a series of black and white drawings of the various stages described. *C. M. Wenyon.*

BRACKETT, S., WALETZKY, E. & BAKER, Margaret. **The Rate of Action of Sulfadiazine and Quinine on the Malarial Parasite:** *Plasmodium gallinaceum*. *J. Pharm. & Exper. Therap.* 1945, July, v. 84, No. 3, 254–61, 2 figs. [13 refs.]

It is agreed that sulphonamides generally exert their full inhibitory effect on bacteria only after a time lag, and similar observations have been made in regard to malarial parasites. The authors suggest that, in general, the rate of action of these drugs may vary inversely with the rate of growth and reproduction of the organism in question. They have tested their view in the case of the relatively slow growing protozoon *P. gallinaceum*, by comparing the results of treatment of this infection in chickens with quinine, which acts quickly, with those following treatment with sulphadiazine or a derivative. Two experiments with similar results were made in which 15 one-week-old chicks were inoculated intravenously with a homogeneous suspension of small forms of the parasite from a donor bird, two days after drug administration had begun. Five of the chickens received a diet containing 0·2 per cent. of sulphadiazine, five others received quinine in similar amount and the remaining five served as controls. The resulting blood-level of sulphadiazine was well above that giving maximum activity in this infection. The course of the infection was followed by making parasite counts immediately after inoculation and 12-hourly thereafter. Differential counts of the parasites were also made in four groups according to size, as a guide to the effect of each drug on growth and reproduction. It was

found that sulphadiazine inhibited growth only after 24 hours, whereas the effect of quinine was very rapid. Treatment of the first generation with the former drug caused a reduction in the number of merozoites, but segmentation was completed and new red cells were invaded without the succeeding development going beyond the four-nucleate stage. The maximum number of parasites was present on the second day of treatment and then gradually declined, whereas in the case of quinine there was no increase of the original numbers. Morphological changes in the parasites occurred more quickly with quinine than with sulphadiazine. In a further experiment with sulphadiazine and its bromo-derivative, action against erythrocytic and exoerythrocytic forms in sporozoite-induced infections was also slow.

The view of the authors, that the time required to cause effective inhibition by slow-acting drugs like the sulphonamides, increases in proportion with the slowness of the rate of growth of the organism, appears to be confirmed, and may be of practical significance in chemotherapy. *J. D. Fulton.*

ZUCKERMAN, A. **In Vitro Tests with** *Plasmodium gallinaceum* **and** *Plasmodium lophurae.* *J. Infect. Dis.* 1945, July–Aug., v. 77, No. 1, 28–59, 4 graphs & 1 pl. [36 refs.]

Having devised a technique for growing macrophages *in vitro* from the blood agranulocytes of chickens, their phagocytic powers against pneumococci in the presence or absence of antipneumococcus opsonic serum was tested. It was found that many pneumococci were phagocyted by the macrophages in the presence of 1 : 1,000 diluted serum, but that phagocytosis was negligible in the absence of immune serum. In addition to being phagocyted, the pneumococci were agglutinated and became adherent to the macrophages. Having demonstrated that opsonization occurred in the case of bacteria, the test was applied to malarial parasites (*P. gallinaceum* and *P. lophurae*) in chickens. It was found that phagocytosis of infected red cells occurred in the presence of hyperimmune homologous serum, but not in the presence of normal chicken serum or of serum from chickens which had merely recovered from an acute initial infection. In addition, as in the case of the bacteria, there was agglutination of the infected cells and their adhesion to the macrophages and to the surface of the glass. These various phenomena involved not only infected cells but also uninfected cells, and any free parasites which were present. It was found that the antibody responsible for stimulating phagocytosis in the case of *P. gallinaceum* was more readily absorbed by normal than by infected red blood corpuscles, an observation which suggests that the absorbing material is a constituent of the normal red blood corpuscles. There was some evidence that opsonization occurred not only *in vitro* but also *in vivo*, for the phagocytic index in the presence of normal serum was higher when the parasitized red cells were collected at the time of the crisis than when they were collected before or after this event. This is a long paper, describing in detail the method of cultivating the macrophages and the various procedures which have to be carried out in order to obtain the data for calculation of the opsonic indices. The appearances of phagocytosis and adhesion are illustrated in a plate of 13 figures. *C. M. Wenyon.*

SEELER, A. O. & OTT, W. H. **Studies on Nutrition and Avian Malaria. III.—Deficiency of " Folic Acid " and other Unidentified Factors.** *J. Infect. Dis.* 1945, July–Aug., v. 77, No. 1, 82–4.

It is shown that *P. lophurae* infections, as judged by parasite counts, are more severe in chicks on a diet deficient in " folic " acid and other unidentified

factors than in those on an adequate diet. The chicks on the adequate diet weighed 150 gm. at three weeks, whereas those on the deficient diet weighed only 100 gm. The continued passage of the strain of parasite through chicks on the deficient diet did not lead to any enhanced virulence, for whenever the strain was inoculated to chicks on adequate diet it behaved as did the control strain kept in serial passages in chicks on adequate diet. It seems evident that the severity of the infection is directly related to the nutrition of the host.

C. M. Wenyon.

Bratton, A. C., Jr. **Continuous Intravenous Chemotherapy of *Plasmodium lophurae* Infection in Ducks.** *J. Pharm. & Exper. Therap.* 1945, Oct., v. 85, No. 2, 103–10, 1 fig.

A method has been devised to avoid the difficulties which occur, owing to incomplete absorption and possible degradation of drugs in the alimentary canal of ducks, when assessing the value of antimalarials administered to them by mouth. It consists in giving a continuous intravenous infusion of a solution of the substance under test over a period of three days. By this means precision in dosage can be attained, and a new method of studying certain problems in chemotherapy is made available. White Pekin ducks infected with *P. lophurae* were used. In order to limit loss of body weight during the test, an average of 250 cc. of infusion fluid per kgm. body weight per day was required. The infusion also served to maintain water balance and nutrition, as ducks cannot retain food in the normal way under the conditions of the test. With larger volumes of fluid than the above, the ducks became oedematous. Details of the method regarding choice of ducks, immobilization of the birds and construction of the pump used should be consulted in the original. Briefly, after immobilization, a 22-gauge needle is inserted into the leg vein of a duck and secured. It is connected to an individual pump, six of which are fitted to a common shaft which makes 7 revolutions per hour. The pumping action is effected by two rollers mounted opposite one another, which compress a rubber tube between them and expel its contents through an outlet, while behind them it is refilled from an inlet, and a continuous flow of fluid can be maintained. The mechanism proved simple and dependable. The drug was dissolved under sterile conditions in an isotonic solution containing 1·2 per cent. of sodium citrate and 4·2 per cent. of glucose adjusted to *p*H 7 by hydrochloric acid. One bird in each series received infusion without drug, and the concentration of the latter for the other birds was calculated after consideration of all the factors. Each bird was infected intravenously from a donor bird with a dose of 3×10^9 parasitized cells per kgm. body weight. Parasite counts and other relevant data were made daily. The minimum effective dose of a drug is defined as that necessary to reduce the number of parasites in a treated bird to half that in a control bird, on the third day, when the experiment ended. The following is the author's summary :—

" 1. A method incorporating a simple rotary injection pump is described for continuous intravenous administration of drugs to ducks infected with *P. lophurae*.

" 2. On the basis of dosage, quinine was more effective at the level of minimum therapeutic response when given intravenously in single daily doses than when given by continuous infusion ; at a high level of response, the converse was true.

" 3. At the level of minimum response, cinchonine was equally effective when given in single daily intravenous doses or continuously.

" 4. Tartar emetic, sodium antimony thioglycollate, and mapharsen were effective in doses at or near the toxic level.

" 5. Penicillin, streptomycin, and quitenine were inactive in the doses employed.

" 6. Summation of therapeutic response was shown by the following two combinations : quinine-cinchonine, and quinacrine-6-chloro-9-(2-diethylamino-ethylamino)-2-methoxyacridine. No summation of response was exhibited by the following combinations : quinine-quinacrine, quinine-pamaquine, and quinacrine-pamaquine. These results suggest that quinine, quinacrine, and pamaquine each possess a different principal mechanism of drug action against *P. lophurae* in the duck." *J. D. Fulton.*

TALIAFERRO, W. H. **Immunity in Malaria.** *Amer. J. Clin. Path.*, 1944, Dec., v. 14, No. 12, 593–7. [25 refs.]

This is an interesting article which might be entitled " An Introduction to the study of Immunity in Malaria." It reviews the knowledge which has been acquired, chiefly from the study of the course of infections, of *Plasmodium brasilianum*, a quartan parasite of New World monkeys, in which the author has played a prominent part.

In the first place the infection increases acutely in intensity till as many as 10 per cent. of the red blood corpuscles are infected. This acute rise is terminated by a parasite decline, at times so sudden as to justify the application of the term crisis. This is followed by a low-grade infection and finally by latency, when no parasites can be found in thick blood films. This latency is interrupted by frequent relapses of varying severity, as occurs with all quartan parasites. In man *P. vivax* has a similar course, but the relapses are less frequent than with *P. malariae*. In the case of *P. knowlesi* in rhesus monkeys, however, the infection develops rapidly during the course of a week till as many as 80 per cent. of the red cells are infected, a result which is nearly always fatal. Occasionally there is a terminal reduction in the number of parasites, but this is insufficient to ward off the fatal issue. By treatment, however, the infection can be reduced so that a condition of low-grade infection, or latency, is reached. In many respects *P. knowlesi*, though of tertian periodicity, resembles *P. falciparum* in man.

Natural immunity to *P. brasilianum* is exemplified by the fact that in first infections 6 to 8 of the 9 merozoites produced at each schizogony are destroyed before red cells are invaded, and of those that succeed in establishing themselves half fail to become mature schizonts. This rate of destruction, which is largely a phagocytic phenomenon, is greatly increased when there is an acquired immunity. The destruction of the parasites is correlated with the phagocytosis of free parasites and infected red corpuscles, chiefly in the spleen, liver and bone marrow. This is particularly marked in the spleen, where filtration of infected cells occurs in the Billroth cords as the result of the action of a specific agglutinin. This is followed by opsonization, which stimulates phagocytosis. In *P. falciparum* infections the infected cells are often agglutinated in other organs, for instance in the brain or placenta, with the result that the phagocytic cells, the macrophages, become active in these unusual sites. The most reasonable explanation of the increased activity of macrophages in acquired immunity is that they and the parasites are influenced by a specific opsonin. It has been shown by COGGESHALL and KUMM [this *Bulletin*, 1938, v. 35, 109] that acquired immunity to *P. knowlesi* can be passively transferred with immune serum. In addition to the development of antibodies during acquired immunity, certain non-specific factors operate. There is a tremendous hyperplasia of microphages and lymphoid cells, chiefly in the spleen and bone marrow. These new macrophages arise from division of pre-existing macrophages or from lymphocytes and monocytes.

The results obtained in the study of monkey malaria have their parallel in human malaria. Certain races have a higher natural immunity than others, while acquired immunity has been clearly demonstrated in man under experimental conditions. Absolute immunity is difficult to acquire, because the immunity is strain-specific. The largest number of strains is found in *P. vivax* and the smallest number in *P. malariae*. In any case when there is an acquired immunity this is largely, if not entirely, associated with a latent or low grade infection, which is liable to relapse at any time. Attempts have been made to induce artificial immunization passively or actively in monkeys and birds with some success, but this procedure offers little promise in man. On the other hand, though there is little to suggest that artificial immunity can be employed to protect man, there is little doubt that it is an adjuvant in drug treatment. The mechanism of relapse is not known, though there is an increasing tendency to ascribe this to the persistence, during latency, of exoerythrocytic stages. These lead to infection of erythrocytes which are destroyed so long as immunity persists. When this immunity subsides the erythrocytic development progresses unhindered, sometimes with serious results.

Other serological changes occur during malarial infections. Thus antibodies, including precipitins, agglutinins and complement-fixing substances, are produced. From the immunological standpoint it is of interest that complement fixation depends on a genus antigen and is thus very different from acquired immunity, which is species and strain-specific. Thus, effective complement-fixing antigens for human malaria have been prepared from *P. knowlesi* and *P. gallinaceum*. The various points mentioned in this summary, in their bearing on the epidemiology, treatment and control of malaria, are discussed in the paper, which is rendered all the more valuable by the author's careful reference to the original papers upon which his statements are based. *C. M. Wenyon.*

BLACKWATER FEVER.

KITCHEN, S. F. & SADLER, G. G. **Report of an Attack of Blackwater Fever subsequent to Induced Malaria.** *Amer. J. Trop. Med.* 1945, Sept., v. 25, No. 5, 379–84, 3 figs.

The authors describe in detail the occurrence of blackwater fever in a female patient, in whom malaria was induced by the introduction of three plasmodial species in succession, *viz.*, *P. vivax*, *P. falciparum*, and *P. malariae*. The *P. vivax* infection was characterized by 27 quotidian paroxysms and spontaneous termination. Occasional parasites were seen in the peripheral blood several months later, but without clinical signs of malaria. Six months after the termination of the *P. vivax* attacks, a natural inoculation of *P. falciparum* was given. The resulting malaria was treated with quinine. Five weeks later *P. malariae* infection was induced by intravenous injections of infected blood. This infection was " terminated by plasmoquin " six weeks later. *P. falciparum* persisted in the peripheral blood in spite of these treatments. There were waves of parasitaemia, with only occasional clinical signs of malaria, for nearly five months. At the end of this period the patient was given two seven-grain doses of quinine in a single day, the last dose being given at 6 p.m. She refused her evening meal and vomited in the early morning. At 7 a.m. it was noticed that she was jaundiced, and by noon her temperature had reached 103°F.

" Late that afternoon " she passed urine containing haemoglobin. There was no rigor associated with the haemoglobinuria. Thereafter the clinical condition was that of typical blackwater fever, and rigors were experienced on the sixth and seventh days. There was no oliguria. The urine during the lytic phase was characteristic in appearance. The reaction is not given. She had only one lytic phase and recovered rapidly. *P. falciparum* was not observed in the blood from the onset until the third day after the subsidence of the fever. Treatment included infusions of 5 per cent. glucose in physiological saline, and 50 per cent. glucose from the first day. Transfusions of 500 cc. of citrated blood were given on the first, second, fourth and seventh days. The red blood cell count was 0·89 million per cubic mm. on the first day, and rose to 1·2 million per cubic mm. on the seventh day. The intake of fluid was carefully balanced throughout against the output in the urine. Sodium bicarbonate was given by mouth in doses of 1 gm. every four hours on the first day.

The chief interest of this case lies in the malarial history. All these strains were well known and had frequently been used for therapeutic purposes. None had any previous record of having been associated with haemoglobinuria.

The authors suggest that the prolonged parasitaemia resulting from the *P. falciparum* malaria may have been an aetiological factor in the production of the haemoglobinuria. They also point out the relationship of quinine administration to the haemoglobinuria attack, as the clinical history of the patient indicates that haemolysis commenced within 12 hours of the administration of the first dose of quinine.

They discuss the treatment from the point of view of replacement of blood by transfusion (they estimate that about three-quarters of the patient's cells were lysed in less than 24 hours), and the administration of alkali. They consider that " the hypothesis that oliguria and anuria are the result of blockage of the renal tubules by haemoglobin degradation products . . . is open to doubt," and conclude that " the indiscriminate use of intensive alkaline therapy " is contra-indicated in blackwater fever.

[The legends for Figures 2 and 3 have been accidentally transposed in the printing of this paper.] *B. G. Maegraith.*

LANCET. 1945, Dec. 1, 701–4, 1 chart. [26 refs.] **Effect of Large Doses of Alkali on Kidney Function.** [Army Malaria Research Unit, Oxford (MAEGRAITH, B. G. *et al.*)]

Intensive alkali treatment is still being recommended for the treatment of blackwater fever, incompatible blood transfusion, and the crush syndrome. The Medical Research Council recommended that in the treatment of wound shock all cases should be given sodium bicarbonate 7 gm. [about 2 drachms] hourly by mouth until the urine turns red litmus blue, but not for longer than 24 hours. Intensive alkali therapy of this kind is accompanied by dangers. Experiments described in this paper show that alkali administered for 24 hours to normal subjects, at less than half the rate recommended above, produces sodium and water retention and disturbance of renal function, which becomes well-marked if the alkali is continued for 72 hours.

Three subjects were given sodium bicarbonate, grains 60, and sodium citrate, grains 60, 2-hourly, one subject for one day, two for three days. All had disturbance of renal function ; in one on the 3-day course this was well marked and led to a three-fold increase of blood urea. All developed sodium and water retention. There was dilution of the blood by about 10 per cent.

The authors consider that large doses of alkali should not be administered in conditions where renal failure may supervene. *Norman White.*

i. Osman, A. A. **Effect of Large Doses of Alkali on Kidney Function.** [Correspondence.] *Lancet.* 1946, Jan. 26, 143–4.
ii. Locket, S. **Effect of Large Doses of Alkali on Kidney Function.** [Correspondence.] *Ibid.* Feb. 2, 180–81.

i. Osman considers the conclusion of the Malaria Research Unit, Oxford, that " large doses of alkali should not be administered in conditions where renal failure may supervene " to be an overstatement. A closely reasoned argument ends thus : " Alkali therapy in renal disease certainly has limitations. It is contra-indicated in the earlier stages of acute nephritis, for example, but I have generally found that when failure with this method is attributed to its unsuitability it is as often due to faulty technique. I submit that large doses of alkali, when properly used, are not necessarily contra-indicated in conditions where renal failure may supervene as a natural development of the disease, but that, given with caution, they will sometimes be the only means of saving or prolonging life."

ii. Locket considers the findings of the Malaria Research Unit, Oxford, to be insufficient to justify the conclusions based thereon. The title of their paper is somewhat misleading as only sodium salts were investigated : potassium and other alkaline salts were not considered. He does not consider the evidence adduced sufficient to justify the deduction that renal function was impaired in the three experimental subjects. *Norman White.*

TRYPANOSOMIASIS.

Stefanopoulo, G., Caubet, P. & Duvolon, S., Mlle. Méningoencéphalite à *Trypanosoma gambiense* (souche neurotrope) observée chez le lapin. [**Meningo-Encephalitis due to *T. gambiense* in the Rabbit.**] *Bull. Soc. Path. Exot.* 1945, v. 38, Nos. 9/10, 271–4, 4 figs. on 2 pls.

The Yaunde strain [this *Bulletin*, 1946, v. 43, 312] of *Trypanosoma gambiense*, in the blood of a rat, was injected subcutaneously into the same rabbit on June 1, 1943, October 19, 1943, November 3, 1943 and November 20, 1943 ; during observation for a year the rabbit showed no signs of illness and its weight remained about the same. On June 30, 1944, paralysis of the hindquarters developed and soon extended to the forelimbs ; the rabbit was killed on July 5, 1944.

At autopsy the spleen was found to be rather small, the urinary bladder was distended with 160 cc. of urine, and the membranes of the brain were much congested. No trypanosomes were seen in fresh blood preparations but they were present in lymphatic gland juice and especially in scrapings of brain tissue in saline. The cerebral membranes showed pachymeningitis with infiltration of lymphocytes and plasmocytes ; perivascular cellular infiltration was seen in the brain. In sections, trypanosomes were fairly numerous in the infiltrated areas of the membranes, and some isolated trypanosomes were present in the brain tissue. The general appearance was similar to what is found in sleeping sickness in man. No morular cells of Mott were seen in the brain but a few were present in the spleen. These findings are shown in photomicrographs.

The authors comment that the neurotropic character of this strain, shown in the mouse and rat, is also apparent in the rabbit. *J. F. Corson.*

ROUBAUD, E. & CAUBET, P. Essais d'immunisation chimio-biologique par le sulfarsénol dans les infections à *Trypanosoma gambiense* chez le rat. [**Attempts at Chemo-biological Immunization in Infections with** *Trypanosoma gambiense* **in the Rat.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 280–84.

Two laboratory strains called "Antwerp" and "Yaunde" respectively [see CAUBET, this *Bulletin*, 1946, v. 43, 312] were used and five experiments were made. The object was to see whether rats developed immunity after treatment of *T. gambiense* infections with sulpharsenol and, if so, to estimate the degree and specificity of the immunity. The rats were infected by intraperitoneal or subcutaneous inoculation, and sulpharsenol was injected as soon as trypanosomes were found in the peripheral blood. After varying intervals the immunity was tested by inoculation of one or other of the two strains of *T. gambiense* and also, in one experiment, by injection of *T. evansi*. The doses of sulpharsenol are expressed as per 100 gm. body weight.

Experiment 1.—Five white rats were inoculated with the Antwerp strain; trypanosomes appeared after 48 hours and 0·03 gm. of sulpharsenol was injected and sterilized the peripheral blood. After 70 days' interval, 15,000 trypanosomes of the Antwerp strain were inoculated intraperitoneally; two untreated rats and two others which had been injected with 0·03 gm. of sulpharsenol 20 and 70 days before, respectively, received, as controls, the same dose of trypanosomes. The untreated controls showed trypanosomes on the 4th day and these were numerous on the 10th day; the control which received sulpharsenol 70 days before behaved similarly, while the control which had received the drug 20 days before was not infected. Of the 5 experimental rats, two behaved like the untreated controls, while the other 3 developed a slow, irregular infection which did not become acute until 13 to 20 days later than in the controls.

Experiment 2.—Three experimental rats and 2 untreated control rats were used. The same procedure as in the first experiment was carried out, but the interval was 90 days and the test dose was 500 trypanosomes. The 3 rats became infected but much more slowly than the controls.

Experiment 3.—A rat of experiment 1 [2 ?] infected with the Antwerp strain in spite of treatment with 0·03 gm. of sulpharsenol 90 days before, was given a second injection of 0·01 gm. of sulpharsenol to reinforce its immunity; after 40 days, 200 trypanosomes of the Antwerp strain were injected. Trypanosomes appeared in the blood on the 5th day but the infection was chronic, with few trypanosomes in the blood, and the rat died on the 80th day, whereas the control rat died of an acute infection on the 60th day.

Experiment 4.—Two rats, infected with the Antwerp strain and sterilized by an injection of 0·015 gm. of sulpharsenol, were tested after 80 days, with a dose of 400 trypanosomes of the Yaunde strain, injected subcutaneously, 2 untreated rats serving as controls, The controls showed trypanosomes on the 12th and 25th days respectively, and the former died with an acute infection after a month. The experimental rats showed trypanosomes on the 23rd and 41st days respectively and the latter died on the 60th day [the times of death of the other control rat and the other experimental rat are not stated].

Experiment 5.—Two rats were injected with 0·03 gm. of sulpharsenol and 75 and 90 days later [75 à 90 *jours*] were infected with the Antwerp strain; they then received a second injection of 0·014 gm. of sulpharsenol, one 10 days and the other 30 days after the appearance of the trypanosomes. Finally they were inoculated with 1,000 trypanosomes of *T. evansi*, one after 30 days and the other after 60 days, two untreated control rats being also injected. All four

animals responded similarly, they showed trypanosomes at 5 to 8 days and died at 11 to 12 days.

The authors remark that the protection was relative only and was apparently specific for *T. gambiense* even though the two strains showed pathogenic differences. There were indications that the destruction of trypanosomes in the tests with injection of 15,000 produced some toxaemia. [It seems to the abstracter that more rats might have been used with advantage.]

J. F. Corson.

ROUBAUD, E. A propos des caractéristiques raciales des souches de *Trypanosoma gambiense.* [**Racial Characters of Strains of** *Trypanosoma gambiense.*] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 290–91.

The author refers to CAUBET's measurements of two strains of *T. gambiense* [see this *Bulletin*, 1946, v. 43, 312] and asks whether such different strains exist in nature or are artificially produced by long maintenance in laboratory animals. The characters of the Yaunde strain have never varied since its isolation and it has never become completely adapted to the blood of small rodents ; this suggests that it is a special racial type with marked neurotropic characters [see below].

Perhaps a selection occurs in man when the infection passes from the early stage in the blood and lymphatic glands to the later stage with involvement of the central nervous system ; these selected races might be spread by tsetse flies in nature. This could explain the variations between the clinical picture and the number of cases [*gravité relative de l'endémie*] often observed in sleeping sickness areas. KUNERT [this *Bulletin*, 1940, v. 37, 17] noted earlier infection than formerly of the nervous system in *T. rhodesiense* infections in man, and Roubaud suggests that this might be explained by the predominance of neurotropic strains ; since, in such infections, trypanosomes are rare in the peripheral blood, the infection would be less transmitted by tsetse, with the result that the amount of sleeping sickness in the area would diminish while the virulence for the nervous system would increase. The question deserves attentive study.

J. F. Corson.

ROUBAUD, E., STEFANOPOULO, G. J. & DUVOLON, S., Mlle. Étude chez le rat blanc d'une souche neurotrope de *Trypanosoma gambiense.* [**A Study of a Neurotropic Strain of** *T. gambiense* **in the White Rat.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 292–6, 3 figs. (2 on 1 pl.) [10 refs.]

During 1943 twelve white rats were infected from guineapigs, mice or other rats, with the Yaunde strain of *T. gambiense.* Three died of the disease after 31, 37 and 54 days and six were killed after 55, 66, 68, 77, 77 and 82 days. The incubation period varied from 4 to 45 days. In the blood the trypanosomes were few, and were often absent, and in only three rats were trypanosomes very numerous at the time of death. In several rats trypanosomes were found at autopsy only in the central nervous system, and, in some, in the lymphatic glands also. Two rats were inoculated intracerebrally and both became paralysed and were killed after 79 days ; one only had shown trypanosomes (very few) in the blood on the 17th and 74th days, but they were very numerous in the brain in both rats. In most cases there was little fever. The body weight remained stationary except in young rats where slight increase occurred, and in infections of long duration where marked wasting took place. Four out of 5 rats in which the infection had lasted for more than two months showed severe nervous symptoms—tremors, staggering, spasms or contractures, paresis or paralysis of the limbs or sphincters.

At autopsy the spleen usually showed little enlargement but the lymphatic glands were very often hypertrophied and sometimes congested. The histological appearances of most interest were in the central nervous system; 7 out of 11 rats showed meningoencephalitis similar to that described in the mouse by STEFANOPOULO and ÉTÉVÉ [this *Bulletin*, 1945, v. 42, 258]. This was seen especially in rats killed after the 60th day; there was intense perivascular infiltration, chiefly of plasmocytes, the neurones frequently showed damage, and neuronophagia was observed, especially in the two rats which were inoculated intracerebrally. Trypanosomes were seen in the brain substance in three cases; in one of those inoculated intraperitoneally, which was killed on the 66th day, the blood showed a few trypanosomes but on the 33rd day only. The other organs showed the usual lesions such as infiltration of the portal canals of the liver, necrosis and degeneration of some hepatic cells, interstitial infiltration of the kidney, many plasmocytes in the spleen, &c. [the heart is not mentioned]. The mulberry cells of Mott were seen in the brain and spleen of some of the rats [see below].

For comparison, 12 rats were similarly inoculated with the Antwerp strain [see CAUBET, this *Bulletin*, 1946, v. 43, 312] which produced acute infections. In only one of 7 rats examined were there lesions of meningo-encephalitis.

The authors refer to the work of others [see this *Bulletin*, 1945, v. 42, 258]; they regard the Yaunde strain as a race of *T. gambiense* with certain fixed characteristics. *J. F. Corson.*

JACKSON, C. H. N. **Pairing of *Glossina morsitans* Westwood with *G. swynnertoni* Austen (Diptera).** *Proc. Roy. Entom. Soc. London.* Ser. A. Gen. Entom. 1945, Dec. 31, v. 20, Pts. 10–12, 106.

It is already known that in cages males of *Glossina morsitans* or *swynnertoni* mate at random with females of either species, and do not select those which are co-specific.

The author has carried out a field experiment to examine the same point. He worked in a spot in which *G. swynnertoni* was abundant and exposed large numbers of pupae of both species in such a way that the adults on emergence were completely free. He caught several hundred pairs and studied the proportion in which the two individuals were of the same or different species. He concludes that even in nature male *G. swynnertoni* mates at random with females of its own species or *morsitans*. The same is probably true of male *G. morsitans* but the numbers were lower and the result not conclusive.

This is remarkable, for it has been shown by VANDERPLANK [this *Bulletin*, 1945, v. 42, 99] that heterogamous matings are barren or nearly so, yet neither species has any mechanism to prevent this occurrence. *P. A. Buxton.*

STEFANOPOULO, G., CAUBET, P. & DUVOLON, S., Mlle. Présence de cellules muriformes de Mott chez les rats infectés de *Trypanosoma gambiense*. [**The Mulberry Cells of Mott in Rats infected with** *Trypanosoma gambiense*.] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 296–300, 4 figs. on 1 pl. [17 refs.]

The " mulberry cells " of Mott were found in the tissues of 2 out of 11 white rats infected with the Yaunde strain of *T. gambiense*; in one rat they were present in the splenic pulp amid numerous plasmocytes. In some mulberry cells the nucleus had disappeared but in others the plasmocyte character of the cell was recognizable, *i.e.* eccentric nucleus, radiating spoke-like chromatin and basophilic cytoplasm with vacuoles or globules, polygonal from mutual pressure, which stained rose-violet with Giemsa's stain. Many intermediate

forms between the plasmocyte and the typical mulberry cell were seen. In sections of the brain of the second rat there were lesions of meningo-encephalitis, intense perivascular infiltration, and trypanosomes in the brain tissue. Mott's cells were seen both in the infiltrations and in the brain tissue ; some were stained a rose colour by Giemsa's stain and others were unstained ; fuchsin stained them a bright red colour. These cells were also present in the spleen of this rat.

Impression films were made of the organs of 6 other rats, similarly infected, and mulberry cells were found in two of them, in the liver and spleen ; these cells stained a pale blue, a difference from those in sections which was noted by REICHENOW (*Ztschr. f. Hyg. u. Infektionskr.*, 1921, v. 94, 266). They were also found in impression films of the organs of guineapigs and mice infected with this strain of *T. gambiense.*

In discussion LAVIER emphasized the value of staining with fuchsin to distinguish Mott's cells from other very similar cells such as macrophages packed with refractive inclusions. He, and others who took part in the discussion, considered that Mott's cells are not pathognomonic of trypanosomiasis. CAPPONI referred to their presence in *T. lewisi* infections of the brown rat in Marseilles, observed by ARGUIE and himself in 1943. *J. F. Corson.*

EAGLE, H. **The Spirocheticidal and Trypanocidal Action of Acid-substituted Phenyl Arsenoxides as a Function of pH and Dissociation Constants.** *J. Pharm. & Exper. Therap.* 1945, Nov., v. 85, No. 3, 265–82, 8 figs. [24 refs.]

In earlier papers Eagle and his associates described the action of a number of substituted phenyl arsenoxides on spirochaetes (*J. Pharm. & Exper. Therap.*, 1940, v. 70, 221) and trypanosomes [this *Bulletin*, 1945, v. 42, 15]. With only a few exceptions, acid substitution caused a marked decrease in activity of the parent arsenoxide, and in the present very interesting contribution Eagle produces considerable evidence for the view that this diminished activity is to be explained on the basis that the ionized salts of these substituted compounds are relatively inactive as compared with the undissociated free acids. This is in line with the facts : (*a*) that the dissociation constants of most of these compounds are such that they would be more than 99 per cent. ionized at *p*H 7·4 ; and (*b*) that increase in the hydrogen ion concentration of the medium in which the tests are conducted results in increased spirochaeticidal or trypanocidal activity.

With regard to (*b*) above, the most obvious effect of increasing the hydrogen ion concentration consists in the formation of undissociated free acid from the ionized salt, *e.g.* :—

$$OAs.C_6H_4.COO^- + H^+ \rightarrow OAs.C_6H_4.COOH$$

If the inference is correct that the undissociated acid is many times more active than the charged ion, there should be a close correlation between the trypanocidal activity of an acid-substituted compound at a given *p*H, and the *p*K of that compound. The higher the *p*K (*i.e.* the weaker the acidic group), and thus the higher the proportion of the undissociated acid at a given *p*H, the greater should be the activity of the compound. This was in fact found by experiment to be the case.

That the striking influence of *p*H on the trypanocidal and spirochaeticidal activity of acid-substituted phenyl arsenoxides is related to the ionization of the acidic group is borne out by a number of other findings. Thus, the activity of the unsubstituted phenyl arsenoxide was largely independent of *p*H. This is also true of the 3-NH_2-4OH phenyl arsenoxide, in which neither of the substituents is strongly acidic. Still more significant is the fact that when an acidic group is

blocked, as by amide formation (*e.g.*, the *p*-$CONH_2$ compound), the trypanocidal activity is no longer dependent on *p*H.

Although the ionized salts of acid-substituted phenyl arsenoxides in general are considered to exercise a relatively low (but variable) degree of activity, it is inferred that in a few exceptional instances (as in the *p*-$(CH_2)_3$ COOH compound ; see this *Bulletin*, 1945, v. 42, 354) the ion is unusually active. This, adding to the activity due to the undissociated molecule, accounts for the unexpectedly high activity of these particular compounds.

Eagle finds sufficient correspondence between theoretical calculation and observed fact to warrant the conclusion that the relative trypanocidal activity of an acid-substituted phenyl arsenoxide is determined by, and is roughly predictable from :—(*a*) the *p*H of the solution ; (*b*) the *p*K of the compound ; (*c*) the trypanocidal activity of the ion. The higher the *p*K, and the lower the *p*H, the greater will be the observed activity of the compound.

Arsenic estimations established that the relative inactivity of the salts of these compounds reflected the fact that they were bound to the trypanosomes to only a minor degree, while the undissociated free acids, like all highly active compounds, were concentrated as much as three-hundred-fold. Variations in *p*H, affecting the relative proportions of ions and undissociated acid, similarly affected the degree to which a given arsenical was bound by the trypanosomes. In a series of acid-substituted phenyl arsenoxides, those with the highest *p*K values (most readily transformed to the undissociated acid on acidification) are the first to show increased activity and increased affinity for the trypanosomes as the reacting mixture is acidified ; while those with strongly acidic groups, which remain as ions at the lowest *p*H tested, are correspondingly unaffected with respect to both activity and combining affinity.

The author discusses the question whether the undissociated acid-substituted phenyl arsenoxides are so strongly bound to trypanosomes because they have an especial reactivity with cellular constituents, such as those containing -SH groups. He concludes, however, that the explanation most probably lies in the fact that the undissociated acids penetrate readily into the interior of the trypanosome cell, whilst the ionized salts are unable to gain admission. He quotes a number of instances, from the literature of widely-separated fields of experimental biology, in support of the general contention that the ions of weak acids (or bases) pass through cell membranes less readily than the corresponding undissociated molecules. A distinguishing feature of the trypanosome-arsenical system here studied lies in the speed at which, and particularly in the degree to which, active non-ionized arsenicals may be concentrated by the trypanosomes. Within ten minutes, the arsenic concentration in the organisms may attain a level several hundred times greater than that of the surrounding fluid. This reflects a rapid diffusion of the arsenical into the organisms, followed by its firm combination with cellular constituents. The arsenical is thereby effectively removed from the diffusion equilibrium, permitting its continued diffusion into the cell. In a sense, the organisms promote their own death by binding the active (undissociated acid) form of the compound, and thus shifting the equilibrium so as to result in the production of yet more of that active form.

E. M. Lourie.

CHORLEY, J. K. **Tsetse Fly Operations. Short Survey of the Operations by Districts for the Year ending December, 1943.** *Rhodesia Agric. J.* 1944, v. 41, No. 6, 412–19. [Summary taken from *Rev. Applied Entom.* Ser. B. 1946, Jan., v. 34, Pt. 1, 15.]

There was little improvement in the position as regards trypanosomiasis of cattle in the Chipinga area of the Melsetter District, on the eastern border of

Southern Rhodesia, in 1943. The total number of tsetse-flies caught on the Rhodesian side of the border was 20, comprising 11 males and five females of *Glossina pallidipes*, Aust., and three males and one female of *G. brevipalpis*, Newst., while 15 males and 13 females of the former and one male and two females of the latter were taken in the clearing on the Portuguese side. Extensive additions were made to the main border clearing. Patrols carried out in Portuguese East Africa and on the border farms indicated that *G. morsitans*, Westw., has not spread much further up the Busi Valley, though individuals were caught about one mile from the border. A light infestation of this species was found in the lower Sabi Valley inside Southern Rhodesia during the year, and trypanosomiasis caused heavy mortality among cattle in the neighbourhood. It is not anticipated that the Sabi and Lundi Rivers will act as effective barriers to the westward spread of the fly as they carry little water in the dry season. The Portuguese Government has declared a large area in Portuguese East Africa along the border east of the Melsetter district an open area for the destruction of all classes of game. This may have highly beneficial results in the control of *G. morsitans* if intensive shooting operations can be organised. The presence of tsetse on the border in the Vila Gouveia area of Portuguese East Africa opposite Inyanga has been notified.

Satisfactory progress was made in the northern areas infested by *G. morsitans*, fly densities over the whole area covered by the operations showing a progressive reduction. No cases of animal trypanosomiasis were recorded from these areas. *G. pallidipes* was found to occur some distance south of its previously known limits in the Sebungwe district. The north-eastern boundary of the area remains heavily infested. Eight more cases of sleeping sickness were recorded from the Urungwe district, three foci of the disease being now recognised. The situation in individual districts is briefly reviewed, and incidental aspects of tsetse control are discussed.

Launoy, L. Albuminurie de la trypanosomose expérimentale à *T. annamense* du lapin ; action des agents trypanocides : I. Action du moranyl employé seul. [**The Action of Trypanocidal Agents on the Albuminuria of Experimental Infection with** *Trypanosoma annamense* **in the Rabbit. I. The Action of Moranyl alone.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 11/12, 347–58, 4 graphs.

Different opinions have been expressed on the importance of the albuminuria which often occurs during the treatment of human trypanosomiasis with Bayer 205 ; as the author could always cause albuminuria in rabbits by infecting them with his strain of *T. annamense* he decided to make experiments to get an answer to two questions : (1) Can moranyl [Bayer 205] cause albuminuria in a rabbit with healthy kidneys ? (2) what effect has treatment with moranyl on the albuminuria of trypanosomiasis ?

He first injected various amounts of moranyl at various intervals into rabbits [4] and estimated the albumin, urea and chlorides in the urine ; slight albuminuria was produced but it soon disappeared. He then infected rabbits [3] with *T. annamense* and treated them with moranyl ; this cured the infection and the albuminuria also disappeared. The figures of the excretion of urea and chlorides gave no indication of serious damage to the kidney having been produced. Details of the experiments are given.

The author concluded that a single dose of 0·02 to 0·05 gm. (even 0·1 gm.) per kgm. does not cause albuminuria, and that doses of 0·02 to 0·05 gm. per kgm., repeated less than four times, at intervals of 1 to 5 days, have little toxic effect on the kidney ; slight albuminuria, oliguria and hypochloruria are produced. With an interval of 14 days between injections, even doses of 0·1 gm.

per kgm. have little toxic action on the kidneys. Trypanosomiasis causes albuminuria 2 to 3 weeks after infection ; it is cured by moranyl before the drug produces its slight irritant effect on the kidneys. These experiments offer no evidence that albuminuria due to trypanosomiasis is a contraindication to treatment with moranyl alone. *J. F. Corson.*

LAUNOY, L. L'albuminurie de la trypanosomose expérimentale à *T. annamense* du lapin : action des agents trypanocides. II. Action de la synergie moranyl-anthiomaline. [**The Action of Trypanocidal Agents on the Albuminuria of Experimental Infection with** *T. annamense* **in the Rabbit. II. The Action of Moranyl and Anthiomaline.**] *Bull. Soc. Path. Exot.* 1945, v. 38, Nos. 9/10, 275–8.

The course of an infection of *Trypanosoma annamense* in a rabbit and the effects of treatment with moranyl and anthiomaline, administered simultaneously, are recorded in full detail. Treatment was delayed until the 47th day after inoculation, the animal being then very ill. The effects were similar to those produced in previous experiments with treatment by moranyl alone [above]. The two drugs were injected together, anthiomaline intramuscularly and moranyl subcutaneously, on the 47th, 51st and 57th days of infection ; on the 60th day an injection of tryparsamide was given. Albuminuria soon disappeared and the rabbit quickly recovered. The author concludes that synergic treatment with anthiomaline and moranyl in suitable dosage is not contraindicated by the presence of albuminuria. *J. F. Corson.*

RODHAIN, J. & RESSELER, R. Essai de différenciation sérologique entre trypanosomes et schizotrypanosomes. [**An Attempt to differentiate serologically between Trypanosomes and Schizotrypanosomes.**] *Ann. Soc. Belge de Méd. Trop.* 1945, June 30, v. 25, Nos. 1/2, 23–37.

The only species of trypanosomes which multiply within the cells of the vertebrate host are *T. cruzi* and *T. pipistrelli* (of the bat) ; they multiply by binary fission, not by schizogony. The authors made serological tests to see whether these species could be distinguished in this way from other species of trypanosomes ; they used *T. brucei*, maintained for several years in mice and rats, *T. cruzi*, maintained in a species of bug (*Reduvius prolixus* (*fumatus*)), and in guineapigs, *T. pipistrelli* in culture and *T. vespertilionis* also in culture, and they had also a rabbit infected with *T. equiperdum*. To obtain specific antisera rabbits were infected with *T. brucei* and with *T. cruzi* and injections of large total amounts (nearly 100 cc.) of cultures of *T. vespertilionis* and of *T. pipistrelli* into rabbits were made during several weeks. The tests used were complement fixation, precipitin reaction and agglutination ; the details are shown in tabular form.

All the precipitin tests were negative ; the complement fixation tests indicated that there was an antigenic relationship between *T. cruzi* and *T. vespertilionis*, less between *T. cruzi* and *T. equiperdum*, and still less between *T. cruzi* and *T. pipistrelli*. The agglutination tests indicated that *T. cruzi* and *T. pipistrelli* had a common agglutinogen which was not present in *T. vespertilionis*.

The only final conclusion was that the two species of trypanosome (*Schizotrypanum*) which multiply within the cells of the vertebrate host cannot be distinguished from other trypanosomes by serological tests. *J. F. Corson.*

BARRETO, A. L. de B. & PONDÉ, A. Doença de Chagas na Bahia. Dois casos parasitologicamente confirmados. [**Chagas's Disease in Bahia : Two Cases.**] *Brasil-Medico.* 1945, Nov. 17 & 24, v. 59, Nos. 46/47, 394–7, 6 figs.

LEISHMANIASIS.

ARMSTRONG, T. G. **Asymptomatic Kala-Azar in Soldiers from Over-Seas.** *Brit. Med. J.* 1945, Dec. 29, 918.

Two cases are described in which fever was slight and toxaemia absent, with the result that kala azar remained for some time unsuspected. The first was in a soldier, 20 years of age, who served for a year in N. Africa before transfer to Salerno and Naples. Eighteen months after leaving N. Africa he was ordered by his sergeant to report sick. On being questioned, he admitted a slow onset during five months of malaise, loss of weight and lassitude, and he was easily fatigued. He was thin and anaemic with a low-grade pyrexia up to 99°F. The spleen was so soft that several weeks elapsed before the author finally decided that it was actually enlarged. In view of a leucopenia and granulopenia, a marrow puncture was performed, with the result that leishmania were discovered. Under stilbamidine treatment the patient made a slow and uneventful recovery.

The second patient returned to England in January 1944 after a year's service in N. Africa, being invalided for diphtheritic polyneuritis. He recovered completely from this, and finally came up for demobilization in September 1945, when he was found to have a greatly enlarged spleen. He made no spontaneous complaint, but on being questioned admitted some dyspnoea on exertion. Examination showed few, if any, signs apart from those attributable to the large spleen, which extended well below the umbilicus. There was a low red cell count and a leucopenia. Marrow puncture showed leishmania, which were also found by inguinal gland puncture.

The author points out that cases of kala azar are likely to be encountered occasionally in England, and that unless the disease is borne in mind it may easily be overlooked. In both the cases described, the patients when pressed admitted minor symptoms of several months' duration, but these they had regarded as so slight as not to warrant attendance at sick parade.

C. M. Wenyon.

SEN GUPTA, P. C. **Complement-Fixation Test with Witebsky, Klingenstein, Kuhn (WKK) or similar Antigens : a Modified Technique.** *Indian Med. Gaz.* 1945, Aug., v. 80, No. 8, 396–8.

In previous papers [this *Bulletin*, 1944, v. 41, 17 ; 1945, v. 42, 358] the author has given an account of his experiences with the complement fixation test for kala azar when the WKK antigen prepared from the acid-fast bacilli of KEDROWSKY and of LLERAS was employed. His further experience has shown that a certain modification of the technique ensures more reliable results. This involves the titration of antigen and complement in a 1 : 25 dilution of serum instead of in saline, and ensures that the titration is made under the conditions that exist in the test proper. It is confirmed that in the absence of severe leprosy and post kala azar dermal leishmaniasis a positive result is indicative of kala azar. A negative reaction is given by only 1 per cent. of all untreated cases in Calcutta, and these appear to be very early cases. The fact that a small number of obvious cases of chronic pulmonary tuberculosis give a positive reaction cannot obscure the diagnosis.

Those who wish to carry out the test must consult the original article for full details of the technique. *C. M. Wenyon.*

FEVERS OF THE TYPHUS GROUP.

LUSK, J. W. **One Hundred and Fourteen Cases of Typhus Fever seen in an Indian Military Hospital in Calcutta.** *Indian Med. Gaz.* 1945, Sept., v. 80, No. 9, 437–45, 4 charts. [21 refs.]

This paper illustrates the difficulty so often experienced in India of determining to which vector-subgroup cases of typhus-group fevers belong. The author saw 114 cases during the months June to December 1943; of these 60 came from a village 80 miles from Calcutta and 54 from Calcutta and its environs.

The salient features have been extracted from the text and tables, and are shown in tabular form [minor inconsistencies occur in the original tables] :—

Serological type	Village cases	Calcutta cases	Total fatal
OXK	55 (4 fatal)	41 (7 fatal)	11
OX19	3	9	0
OX2	0	1 (fatal)	1
Clinical and P.M. evidence ...	2 (2 fatal)	3 (3 fatal)	5

Louse transmission seems to have been excluded, so that although the great majority of the cases can be assumed to have been mite-borne, there may have been 12 flea-borne, and possibly one or more tick-borne cases.

No local lesion was seen in any case, and only two patients showed appreciable lymphadenitis. A pronounced rash occurred in the *OX2* case, in which also there was troublesome bleeding from the gums. In 14 other patients, all of the *OXK* type, a faint macular rash was detected.

[It would not be helpful to summarize the clinical and other features in detail because these would not be comparable with those seen in purely mite-borne outbreaks.] *John W. D. Megaw.*

SNYDER, J. C., ZARAFONETIS, C. J. D. & LIU, W. T. **The Susceptibility of the Rodents, *Gerbillus gerbillus* and *Gerbillus pyramidum*, to Experimental Typhus Infection.** *Proc. Soc. Exper. Biol. & Med.* 1945, June, v. 59, No. 2, 110–12.

Two rodents, *Gerbillus gerbillus* and *Gerbillus pyramidum*, especially the former, were found highly susceptible to inoculation with the rickettsiae of louse-borne and murine typhus. Inoculation with large doses of either strain, by nasal, intraperitoneal, or intravenous routes, caused death in most of the animals within 3–8 days. The intravenous route was found most satisfactory.

Animals which had recovered from sub-lethal doses of either strain of rickettsia were immune to heavy doses of infection by both strains.

G. gerbillus, after subcutaneous inoculation with two relatively small doses of louse-borne typhus vaccine, became immune to a lethal dose of the same strain of rickettsiae.

After sub-lethal doses of either strain of infection, complement-fixation antibodies were found for the homologous strain; there was a slight degree of cross fixation.

The Weil-Felix reaction was negative in the few animals tested after infection.

G. gerbillus was slightly less susceptible to fatal infection than the Eastern cotton rat, *Sigmodon hispidus hispidus*. No gerbille of either species was found naturally infected. The animals used in the experiments were trapped in the desert near Cairo, where they abound. *John W. D. Megaw.*

ZARAFONETIS, C. J. D. **The Susceptibility of the Rodents, *Gerbillus pyramidum* and *Gerbillus gerbillus*, to Experimental Tsutsugamushi Infection (Scrub Typhus).** *Proc. Soc. Exper. Biol. & Med.* 1945, June, v. 59, No. 2, 113–16.

Four strains of rickettsiae isolated from scrub-typhus patients, in Imphal, Calcutta and Ceylon, were transmitted with equal success through series of passages, maintained mostly by intraperitoneal inoculation, in the two species of gerbilles used in the experiments described in the immediately preceding paper. When large doses of infected peritoneal washings were given by subcutaneous, intraperitoneal, or intravenous injection, death invariably resulted in 9–12 days and numerous rickettsiae were found in the abundant peritoneal and pleural exudate. The smears were stained with a 1 per cent. solution of methylene blue; this was found more satisfactory for *R. orientalis* than Macchiavello's stain, which coloured the organisms blue instead of the fuchsin-red tint taken on by other species of rickettsiae.

The gerbilles are regarded as suitable substitutes when white mice are not available. *John W. D. Megaw.*

ANDREWES, C. H., KING, H. & WALKER, J. **Experimental Chemotherapy of Typhus. Anti-Rickettsial Action of *p*-Sulphonamidobenzamidine and Related Compounds.** *Proc. Roy. Soc.* Ser. B. 1946, Jan. 10, v. 133, No. 870, 20–62. [52 refs.]

This highly technical paper deals with the chemistry of *p*-sulphonamidobenzamidine and many other related compounds with anti-rickettsial activity, including no fewer than 13 discovered in the course of the investigation. The biological aspect of the work has already been described in an article by ANDREWES, KING, VAN DEN ENDE and WALKER [see this *Bulletin*, 1945, v. 42, 20]. The present paper will be of special interest only to workers engaged in chemotherapeutical research, and these will wish to read it in original.

John W. D. Megaw.

DAVIS, W. A. [U.S.A. Typhus Commission.] **Typhus at Belsen.** 29 mimeographed pp., 4 tables & 1 map. [Field Headquarters APO 887, U.S. Army, dated 26 July, 1945.]

This description of the work of the Typhus-Control Unit at Belsen Camp is necessarily a gruesome document. The author, who belonged to the U.S.A. Typhus Commission, was placed in sole charge of the Unit on April 21, 1945. The horrible conditions prevailing in the Camp are now so widely known that no reference to them is needed.

The Unit began its work about five days after contact had been made with the Camp, and completed its task on May 25. It dealt solely with preventive measures, which consisted almost entirely in the systematic disinfestation of the internees with DDT powder and the inoculation with typhus vaccine of the personnel engaged in the work. For most of the time the DDT powder available was of 5 per cent. strength; the 10 per cent. strength, urgently asked for by the author, was delayed in arrival.

The degree of overcrowding that prevailed is shown by the fact that in many rooms at least 24 persons were confined in a space " approximately 6 ft. wide, 12 ft. deep and 8 ft. high "; the occupants were not allowed to go out except for a few hours in the afternoon, they lay two in each bunk and on the floor.

On the entry of British troops about 45,000 internees were alive in Camp 1, and about 10,000 corpses were still unburied. Among the living there were about 5,000 cases of famine oedema, 3,500 of typhus, 20,000 of enteritis, and 10,000 of tuberculosis. In Camp 2 there were 16,000 internees.

The first task was to bury the dead, erect latrines, clear away excrement, establish a water supply, and begin the evacuation of the " fit ".

A large 10-gun power duster was assembled by April 22 ; by April 30 nearly 50,000 persons had been dusted in Camps 1 and 2, and all persons sent to hospital (11,890) had been bathed and disinfested before admission.

The effect of disinfestation was spectacular ; the last attack of typhus among the internees was on May 14, so that obviously the epidemic had been brought to an abrupt end. This result was strong evidence that transmission had been by living lice rather than by the dried faeces of the insects, and it was brought about in spite of failure to achieve 100 per cent. destruction of the lice.

Cases continued to occur among the attendants on the sick, but though the patients had been disinfested the possibility of transmission by live lice could not be excluded. Among 96 British medical students who worked at the camp there were six cases of the disease, though all had been inoculated and dusted. The average duration of the fever among British workers at Belsen was 8·5 days, and none of the attacks was severe.

Among 49 German-Army nurses engaged in washing and dusting the sick before entry to hospital there were 32 cases. The German medical officer in charge of the nurses refused to allow them to be inoculated on the ground that this had already been done, but afterwards it was admitted that they had not received any vaccine.

The only group of helpers who remained free from infection were the members of the American Field Service Unit ; the author seems to suggest that their special immunity was due to their having received the Cox type of vaccine, whereas the others had received the Craigie type. [In the absence of information regarding the degree of exposure to risk, the time of inoculation, and possible earlier vaccination, this suggestion should be received with reserve.]

About 10 persons were disinfested with each pound of powder.

John W. D. Megaw.

Silva, R. & Kopciowska, Léonie. Contaminations de laboratoire chez les individus vaccinés, dans le typhus exanthématique. [**Laboratory Infection with Exanthematic Typhus in Vaccinated Persons.**] *Bull. Soc. Path. Exot.* 1945, v. 38, Nos. 11/12, 320–23.

A laboratory worker had received nine doses of vaccine at intervals of about seven days. The first seven doses were of murine, and the last two of bivalent, vaccine. Eight days after the end of the course of vaccination he was attacked by typhus fever of a very mild type. The complement-fixation titre with classical antigen rose to 1–640, and with murine antigen it rose to 1–160, so the diagnosis was classical typhus.

Another worker had received five doses of bivalent vaccine, and nearly five months later he had a very mild attack in which the complement-fixation titre rose to 1–640 with both classical and murine antigen. On the strength of this the diagnosis of " mixed infection " was made.

[The term mixed infection presumably means an infection due to *Rickettsia prowazeki* and *R. mooseri* ; if so, most observers would hesitate to regard the complement-fixation findings as satisfactory evidence on which to base so inherently improbable a diagnosis, especially in the case of a person who had received bivalent vaccination.] *John W. D. Megaw.*

PLOTZ, H. & WERTMAN, K. **Modification of Serological Response to Infection with Murine Typhus by Previous Immunization with Epidemic Typhus Vaccine.** *Proc. Soc. Exper. Biol. & Med.* 1945, June, v. 59, No. 2, 248–51.

The responses to the complement-fixation and rickettsia-agglutination tests are normally very consistent among persons attacked by epidemic (louse-borne) and endemic (flea-borne) typhus fevers. Much higher titres are observed in tests made with the homologous than in those made with the heterologous antigen. The authors found that among patients who had previously been protected by epidemic-typhus vaccine, anomalous responses were obtained, as can be seen from the table compiled from three tables illustrating the paper. The first two examples in the table show the kind of responses usually obtained in unvaccinated persons about the end of the third week of attacks of epidemic and murine typhus; the other entries relate to patients suffering from murine typhus, who had been vaccinated during the previous two years with the epidemic-typhus vaccine used in the U.S.A. Army. The interval since vaccination is shown in brackets.

	Disease	Day of disease	Weil-Felix titre		Complement-fixation titre		Rickettsia agglutination titre	
			OX19	*OX2*	Epid.	Murine	Epid.	Murine
Unvacc. ...	Epidemic T.	19	2,560	80	640	0	5,120	1,280
Unvacc. ...	Murine T.	20	160	0	0	160	640	10,240
Vacc. (2 y.) ...	Murine T.	21	2,560	0	640	320	80	1,280
Vacc. (3 m.) ...	Murine T.	22	160	0	1,280	640	320	640
Vacc. (1 m.) ...	Murine T.	21	320	0	160	160	5,120	10,240
Vacc. (3 m.) ...	Murine T.	18	1,280	0	640	160	5,120	10,240
Vacc. (?) ...	Murine T.	15	640	320	80	10	1,280	5,120
Vacc. (2 m.) ...	Murine T.	24	80	40	320	320	1,280	5,120

The anomalous response persisted till late convalescence, for example, in two patients tested on the 159th and 70th days, respectively, in both of whom the epidemic complement-fixation titre was 1–320 and the murine titre 1–160, though the murine rickettsia-agglutination titres were 1–2,560 and 1–1,280 respectively, and the corresponding epidemic titres were 1–320 and 1–160.

No such anomalous reactions were observed in persons suffering from various other diseases due to virus, bacterial, or protozoal infections, so the authors conclude that the unusual reactions are due to previous immunization with rickettsial products, followed by infection with murine rickettsiae.

It was observed that previous immunization with epidemic-typhus vaccine had little or no effect on the severity of the subsequent attacks of murine typhus. *John W. D. Megaw.*

RUMREICH, A. S. & KOEPKE, Jean A. **Epidemiological Significance of Seasonal Variations in Rodent-Ectoparasite Distribution.** *Pub. Health Rep.* Wash. 1945, Nov. 30, v. 60, No. 48, 1421–8, 2 figs. [18 refs.]

The object of this investigation was to obtain epidemiological evidence of the relative importance of the various potential vectors of endemic typhus. Very large numbers of rats were trapped throughout the year and their ectoparasites were identified and counted. The localities investigated were; Jacksonville, Florida; Mobile, Alabama; and Honolulu; the numbers of rats examined in these places were 4,663, 6,123 and 6,382 respectively.

In Jacksonville the prevalence of *Xenopsylla cheopis* and of the mite *Laelaps hawaiiensis* corresponded to the incidence of endemic typhus, when allowance was made for a time lag of one month in the occurrence of the disease. Both parasites were almost equally numerous.

A similar correspondence existed between *X. cheopis* and endemic typhus in Mobile, but the correlation with *L. hawaiiensis* was practically nil; *X. cheopis* was more abundant than the mite in the ratio of 1·7 to 1·0.

The findings in Honolulu were quite different; the prevalence of *X. cheopis* was not correlated with the incidence of the disease, and although some correlation occurred in the case of *L. hawaiiensis* it was not statistically significant. The mite was more abundant than the flea in the ratio of 3·5 to 1·0.

The rat mite, *Liponyssus bacoti*, which experimentally is a proved vector, was found in insignificant numbers in Mobile and Honolulu; it was so erratic and contraseasonal in Jacksonville that it could not have been an important vector. None of the other ectoparasites of the rat could be suspected of being a vector on the evidence obtained.

The imperfections incidental to the survey are discussed, but after giving the fullest weight to these, the authors are of opinion that *X. cheopis* "may be accepted as at least an important vector in Jacksonville and as the principal vector in Mobile," but the available evidence does not support the assumption that this flea plays an equivalent rôle in Honolulu. The mite *L. hawaiiensis* is dismissed on the ground that it has not been shown to be infectible either in nature or experimentally.

[The findings on which the authors have based their conclusions cannot be abstracted, the whole paper deserves close study by all who contemplate making an investigation of the same kind; a vast amount of highly skilled work has been involved in its production, and few workers can hope to command either the opportunity or the special knowledge needed for carrying out so complete a survey.

The authors have not referred to the question whether the lack of correlation between the prevalence of *X. cheopis* and typhus fever in Honolulu is actually opposed to the assumption that the flea is the principal or sole vector in the area. It may be impossible to give an answer to this question because, if a vector were present in numbers sufficient to maintain transmission, the prevalence of the disease might well depend on other factors as well as on the density of population of the vector.] *John W. D. Megaw.*

TATTERSALL, R. N. & PARRY, T. E. **An Outbreak of Typhus Fever (OXK) in India.** *Indian Med. Gaz.* 1945, Sept., v. 80, No. 9, 433–7, 2 figs. on 1 pl., 2 text figs. & 4 charts.

This report deals with 121 cases of "typhus fever (OXK)" occurring in a British regiment during October and November 1943, in an area "adjacent to Burma."

The regiment went into camp in the affected area on October 11, 1943, and remained till November 2. The first case occurred 9 days after arrival, and the last 17 days after departure from the area.

Some of the chief clinical features were as follows (the figures in brackets show percentage incidence):—frontal headache with photophobia (100); sore throat (63); eschar (9); a rash was seen in 79 cases, it was macular in 39 and papular in 40; generalized adenitis (95); mental apathy (99), sometimes amounting to coma; cyanosis and flushing (95); chest signs (88); conjunctival injection (59); deafness (33); and secondary fever (17).

The Weil-Felix (OXK), titre usually reached 1–200 by the 13th day. The maximum readings were obtained between the 13th and 22nd days, and after

this the titre tended to fall. The Dreyer technique and standard army suspensions were used. The average leucocyte count in the second week was 5,400 per cmm. The average differential count was: polymorphonuclears, 47 per cent.; lymphocytes, 46 per cent.; and monocytes, 6 per cent. Eosinophilia was common in the 4th and 5th weeks. There were 11 deaths.

A poor response to the exercise tolerance test persisted for three to four weeks [presumably after defervescence].

Post-mortem examinations were made in all the fatal cases. The right side of the heart was dilated in ten; there was extreme pulmonary congestion in ten; pneumonia in six; enlarged mesenteric glands in all; congestion of the meninges and surface of the brain in all; and petechial haemorrhages, in the stomach, ileum, caecum or colon, in five. *John W. D. Megaw.*

GRIFFITHS, J. T., Jr. **A Scrub Typhus (Tsutsugamushi) Outbreak in Dutch New Guinea.** *J. Parasitology.* 1945, Oct., v. 31, No. 5, 341–50, 5 figs.

In this outbreak there were 931 cases with 34 deaths, among U.S.A. troops who landed on July 30, 1944, on a coast in the Vogelkop Peninsula of Dutch New Guinea.

More than 500 of the cases were contracted in semi-cleared areas covered with knee-high grass growing on moist soil; there were also scattered cocoanut, banana, papaya and kapok trees, remains of village sites, small plantations, and native gardens.

The incidence was low (26 cases) in two islands covered with cocoanut trees among which a dense undergrowth had sprung up so that only "small amounts of grass and scrubby growth" remained. The scantiness of the grass was suspected of being the cause of the smallness of the mite population.

Another area consisted of a strip of grass and ground-clinging vines along the beach, backed by forest; from this environment there were 90 cases, but the incidence was low compared with that in the first area. Most of the military base consisted of dense forest where no grass grew; in this area no cases occurred, though scrub itch was common.

The incubation period was 7–17 days; the outbreak rapidly reached its height by August 15; about this time an average of 45 cases was being admitted daily, but soon a rapid decline set in; by the middle of September the daily admissions had fallen to three or four, and at the end of the month an average only of one case daily was occurring.

The removal of grass and undergrowth from a site was found an effective method of control; when the top soil had dried out the area was considered safe. There was no evidence that rat control was of any practical value. Impregnation of clothing with a soap emulsion containing dimethyl phthalate was strikingly successful.

Some of the clinical features observed in a sample group of 275 patients were as follows (the figures show percentage incidence): eschar with local lymphadenitis (92); photophobia (45); insomnia (75); generalized lymphadenopathy (95); and measly rash on body and limbs (28). The commoner sites of the eschar were the axillary region (24), scrotum (20), thighs (11), inguinal region (8), and penis (8). The temperature usually fell by lysis (70); when it fell by crisis (30) the attacks were much less severe on the whole, and the convalescence was more rapid.

Of the 34 deaths in the whole outbreak (3·65 per cent.) 18 occurred on the 11th to 14th day, 10 on the 15th to 18th day, and 6 on the 20th to 26th day from the onset. *John W. D. Megaw.*

DESHMUKH, M. D. **Clinical Picture of Scrub Typhus in East African Troops on the Burma Front.** *East African Med. J.* 1945, Nov., v. 22, No. 11, 360–67.

During the "last quarters" of 1944, 615 cases were treated in a General Hospital for East African troops in Burma. The author describes some features of the disease as seen in 200 cases selected for their severity and interesting complications. The incubation period was two to three weeks.

Generalized lymphadenitis was usual. A primary sore was seen in 35 cases, and a rash, usually inconspicuous and macular, in 15. Nearly all the patients complained of pains in the bones and joints. Eight patients became insane, two of them appeared unlikely to recover, and one, "having cut his abdomen open with a razor blade, ripped off the intestines from the mesentery."

Various types of neuritis occurred, affecting the auditory nerve in eight cases, the facial in two, the laryngeal in two, the optic in one, nerves of the legs in six, and of the arms in one. Abscesses after injections were common, there was phlebitis of the femoral vein in two cases, and suppurative parotitis in one. Of the 615 patients 12 died; nine of these had been evacuated between the 6th and 11th days; when transfers after the 4th day were forbidden the fatality rate became negligible.

The naked-eye post-mortem findings were uniform and "rather disappointing": the lungs were congested; the heart was flabby but normal in size; the spleen was enlarged, soft, and friable; the kidneys were congested; the mesenteric glands were enlarged; there were usually pin-point haemorrhages in the stomach and intestines; and there was congestion of the superficial vessels of the brain. The microscopic findings were: endothelial swelling and proliferation in the capillaries of the brain, but no perivascular aggregation of cells was seen; the cells of the renal tubules were swollen and necrosed; and there was endothelial proliferation in the lymph glands.

The Weil-Felix reaction (*Proteus OXK*) was of the usual type.

John W. D. Megaw.

SOKOLOW, M. & GARLAND, L. H. **Cardiovascular Disturbances in Tsutsugamushi Disease.** *U.S. Nav. Med. Bull.* 1945, Dec., v. 45, No. 6, 1054–68, 5 figs. [14 refs.]

The after effects of scrub typhus on the cardiovascular system were studied in 35 convalescent patients at an average interval of 4·7 months after the onset of the attacks. All the patients had been "ambulatory" for at least six to eight weeks, many of them for three months.

The exact significance of the findings cannot be estimated, because there was no information to show what proportion of the total number of convalescents was represented by the patients. It was thought possible that the 35 men formed a relatively small percentage of the total. [Apparently they had been sent for special observation and treatment.]

The special symptoms were: weakness, dyspnoea, palpitation of varying degree, and precordial pains. Electrocardiograms showed no gross abnormalities in any case, but minor defects were found in seven cases. There was X-ray evidence of definite cardiac enlargement in four patients, of whom one had appreciable enlargement of the left ventricle. In 14 of the patients roentgenkymograms showed abnormal contractions, affecting the left ventricle in all but one of them.

Decrease in the vital capacity was seldom pronounced, but 75 per cent. of the patients could not hold their breath for the normal time of 45 seconds, and in seven cases the maximum time was only 20 seconds.

Two-thirds of the men had tachycardia on standing, and nearly half of them had abnormally high pulse rates after mild exercise tests. About 75 per cent. had dyspnoea, palpitation, fatigue and dizziness after the standard exercise-tolerance test.

All the evidence went to show that the defects were due to scrub typhus, because a group of men who had been exposed to malaria, dysentery and other adverse conditions to the same degree were found free from these defects.

The pathogenesis of the condition is discussed ; it is left an open question whether the chief factor was myocarditis, peripheral vaso-motor instability, or, perhaps, lesions of the cerebral vaso-motor centres.

Progressive improvement resulted from treatment. The conclusion reached is that convalescence in many cases of tsutsugamushi disease is protracted, and that disabling circulatory disturbances may persist in some cases up to at least six months from the onset. *John W. D. Megaw.*

MURRAY, E. S., ZARAFONETIS, C. J. D. & SNYDER, J. C. **Further Report on Effect of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease (Scrub Typhus).** *Proc. Soc. Exper. Biol. & Med.* 1945, Oct., v. 60, No. 1, 80–84.

Experiments are described which demonstrate that para-aminobenzoic acid can greatly reduce the fatality rate among gerbilles inoculated with lethal doses of *Rickettsia orientalis*. The sodium salt (NaPAB) was used, and was given by a combined method—orally with food, starting a few hours after intraperitoneal inoculation with the rickettsiae, and also subcutaneously, starting on the 4th or 5th day after inoculation.

The results obtained in the whole series of experiments were that among 130 control animals only two (1·5 per cent.) survived, whereas among 128 treated animals 105 (82 per cent.) survived. Most of the animals received 10–1,000 " certainly lethal doses " of rickettsiae, and very few of the animals that died in spite of treatment showed the typical lesions of the disease at autopsy. The strains of rickettsiae used in the trials originated from Calcutta, Ceylon, Imphal, and New Guinea.

Details of the preparation of NaPAB and of the method of administration are given in the paper. *John W. D. Megaw.*

SNYDER, J. C. & ZARAFONETIS, C. J. D. **Effects of Para-aminobenzoic Acid in Experimental Tsutsugamushi Disease (Scrub Typhus).** *Proc. Soc. Exper. Biol. & Med.* 1945, Oct., v. 60, No. 1, 115–17.

This paper contains a description of experiments carried out before those referred to in the preceding abstract. PABA was given, mixed with the food, to gerbilles after intraperitoneal injections of 100 to 1,000 lethal doses of *Rickettsia orientalis*, but the only result was a slight prolongation of the survival time.

The early experiments on the combined oral and parenteral treatment with sodium salt of PABA (NaPAB) are also described ; in these the survival rates after 10–100 lethal doses of the Ceylon strain were 87½ and 62½ per cent. respectively. *John W. D. Megaw.*

ROSE, H. M., DUANE, R. B. & FISCHEL, E. E. **The Treatment of Spotted Fever with Para-Aminobenzoic Acid.** *J. Amer. Med. Ass.* 1945, Dec. 22, v. 129, No. 17, 1160–61, 1 chart.

Para-aminobenzoic acid (paba) has already been found effective in the treatment of louse-borne typhus in man by YEOMANS and his colleagues [see this

Bulletin, 1945, v. 42, 201] and there is evidence of its beneficial action on animals experimentally infected with the rickettsiae of epidemic, murine, and tick-borne typhus.

The authors now report a case in which the drug appears to have had a striking effect on a patient suffering from " spotted fever " [Rocky Mountain spotted fever].

The drug was given by the mouth from the 4th day ; the initial dose was 4 gm. ; this was followed by doses of 2 to 2·5 gm. every two hours in 25 cc. of chilled 5 per cent. solution of bicarbonate of soda. There was a tendency to nausea, but otherwise the drug was without unpleasant by-effects. The total daily dosage was 25, 30, 26, 20 and 8 gm. The blood concentration, measured by a method used for sulphonamides, was 6·6 mgm. per 100 cc. on the 2nd day of treatment, 16·4 on the 4th, and 18·6 on the 5th day. Within 24 hours of the commencement of this treatment there was a remarkable clinical improvement in the patient's condition and the temperature began to fall rapidly : from nearly 106°F. on the 2nd day of treatment it fell to 99·2° on the 4th day, and thereafter it ranged between 99° and 101°F. for five days, after which it remained normal.

Although the authors admit that one case is not enough to justify a dogmatic conclusion, the course of the attack strongly suggests that the drug had a strikingly beneficial effect. *John W. D. Megaw.*

HAMILTON, H. L. **Effect of p-Aminobenzoic Acid on Growth of Rickettsiae and Elementary Bodies, with Observations on Mode of Action.** *Proc. Soc. Exper. Biol. & Med.* 1945, June, v. 59, No. 2, 220–26, 3 figs.

Details are given of experiments which showed the inhibiting effect of *p*-aminobenzoic acid (paba) on the growth of rickettsiae of Rocky Mountain spotted fever in infected yolk sacs.

Doses of 2 mgm. of paba injected into the yolk sacs immediately before inoculation caused a considerable delay in the death of the embryo chicks and enabled some of them to hatch out. As many as 46 per cent. of the chicks survived after an infection which killed all the controls within five days. The drug, therefore, appeared to be more effective for the Rocky Mountain spotted fever rickettsiae than for those of louse-borne and murine typhus.

The drug was found less effective against other strains of tick-borne typhus in the following order of diminishing efficiency—Brazilian tick-borne typhus, Colombian tick-borne typhus, South-African tick-bite fever, and boutonneuse fever.

Corresponding tests were carried out on eggs infected with Q fever, tsutsugamushi disease, lymphogranuloma inguinale, and psittacosis, but no inhibiting effect was observed in any of these.

The mode of action of paba is discussed, and the conclusion is reached, after experiment, that any change in the molecular grouping or the size of the molecule abolishes the inhibitory action of the drug, so that the action may be on an enzyme system. *John W. D. Megaw.*

BELL, E. J. & PLOTZ, H. **Infection and Immunity following the Intracutaneous Inoculation of Scrub Typhus.** *Proc. Soc. Exper. Biol. & Med.* 1945, June, v. 59, No. 2, 143–4.

Rabbits, guineapigs and hamsters were inoculated intracutaneously with peritoneal exudate from a guineapig infected with scrub typhus. After 5–10 days indurated patches appeared at the site of the injection and persisted for 2–8 days. The animals were found immune when challenged, 13–20 days

after inoculation, with infected material which caused the usual reaction in control animals. The experiments demonstrate the production of active immunity against scrub typhus in experimental animals.

John W. D. Megaw.

FULTON, F. & JOYNER, L. **Cultivation of *Rickettsia tsutsugamushi* in Lungs of Rodents. Preparation of a Scrub-Typhus Vaccine.** *Lancet.* 1945, Dec. 8, 729–34, 3 figs. [21 refs.]

Previous attempts to produce a scrub-typhus vaccine had failed; yolk-sac cultures had yielded irregular and poor growths, and even in the few cases in which rich cultures were obtained little antigen was found. Although a former attempt to obtain mouse-lung vaccine had also been reported to have failed, the authors succeeded in adapting *Rickettsia tsutsugamushi* to regular growth in the lungs of mice, and still better results were obtained by using cotton rats.

Full details are given of the technique employed; precautions to prevent infection among workers included the use of the van den Ende box during the intranasal inoculation of the mice and the grinding of infected tissues. Dust masks were worn, and before opening the box the air of the room was sprayed with lactic acid in the form of aerosol mist. Four workers during 18 months remained free from respiratory infection, but one was infected by the bite of an animal that had just been inoculated.

The original inoculum was obtained from a lyophil-dried yolk-sac culture which was injected intraperitoneally into mice after suitable preparation. The resultant peritoneal exudate was instilled intranasally into mice; and after several passages the animals began to die, with total consolidation of the lungs, on the fifth or sixth day.

At this stage the rickettsiae in lung smears became smaller and ceased to take up the Giemsa or other stains. This difficulty was overcome by a special staining method of which details are given; but, as will be seen from the next abstract, this method was later superseded. Another trouble arose from bacterial invasion of the lungs of the mice, but this was controlled by intraperitoneal injections of sulphathiazole.

The strain was passed 26 times through mice and from about the seventh passage it remained constant. The identity of the strain after passage was established by animal-inoculation and complement-fixation tests, but conclusive evidence on the subject was obtained through the occurrence of a typical attack of scrub typhus in the worker mentioned above who was bitten by a cotton rat which had just been inoculated intranasally with material from the 22nd lung passage. The incubation period was 14 days and the OXK agglutination titre rose from 1–160 to 1–50,000.

The method found most suitable for titrating the mouse-lung suspensions was the one described by ANDREWES and his co-workers [see this *Bulletin*, 1945, v. 42, 20].

In a search for a more susceptible animal than the mouse, the cotton rat (*Sigmodon hispidus hispidus*) was found most suitable, though the hamster was nearly as good. Rabbits, black and white rats, and guineapigs were not satisfactory. The cotton rats died on the 4th or 5th day with total consolidation of the lungs; smears from the lungs contained large numbers of rickettsiae, many of which were present in dense masses in large mononuclear cells.

In the preparation of vaccine the lungs were ground with glass powder and suspended in buffered formol-saline; coarse débris was removed by low-speed centrifugation; the fluid was then centrifuged at 10,000 revolutions per minute for 20 minutes and the deposit was resuspended in buffered formol-saline. The lungs of six cotton rats were used to make 60 ml. of the vaccine, which was

tested in the following way :—A group of 50 Swiss mice received three doses each of 0·25 ml. intraperitoneally at weekly intervals. Ten days after the last dose they, and 50 unvaccinated mice, were challenged, in groups of eight, with intraperitoneal injections of spleen substance from infected mice. The dose of infected material was graduated by dilution in ten-fold steps from 10^{-1} to 10^{-6}. The numbers of mice dying within 25 days after being challenged are shown. The infecting doses are arranged in descending series, beginning from the left :—

Vaccinated ...	5	3	2	1	3	0
Controls ...	8	8	7	8	6	4

After vaccination by the subcutaneous route with similar doses, the comparable figures for four groups of 10 mice each were as follows :—

Vaccinated ...	7	6	2	5
Controls ...	10	9	8	4

The significance of the results is discussed. It is admitted that the vaccine seems to give poor protection compared with the results obtained in mice protected against epidemic typhus by epidemic type vaccine, but in view of the intense susceptibility of the mouse to scrub typhus it was thought that this impression might be misleading ; as epidemic and scrub typhus in man are so similar in their clinical features, there seems some reason to hope that the vaccine against the latter may prove as effective as the epidemic type vaccine.

The doses which have been suggested for trial in human beings are three of 1·0 ml. each given at weekly intervals, and a " booster " dose of 1·0 ml. every three months.

The authors finally point out that " without a field trial, it is impossible to decide whether this vaccine will be of any value in man."

John W. D. Megaw.

Buckland, F. E., Dudgeon, A., Edward, D. G. ff., Henderson-Begg, A., MacCallum, F. O., Niven, J. S. F., Rowlands, I. W. & van den Ende, M., with H. E. Bargmann, E. E. Curtis & M. A. Shepherd. **Scrub-Typhus Vaccine : Large-Scale Production.** *Lancet.* 1945, Dec. 8, 734–7, 8 figs.

The authors tell the remarkable story of " Special Operational Store-Tyburn," which was organized for the large-scale preparation of scrub-typhus vaccine, on the lines described in the immediately preceding paper, with the object of carrying out field trials in the Far-Eastern war zone.

A large laboratory was designed and constructed at Frant in Sussex. Housing for the breeding colonies of cotton rats was ready within 31 days, and the complete laboratory was opened on May 31, 1945, within 109 days of the decision to start the operation. This feat was made possible by the military priority accorded to the scheme.

All the rooms in which there was risk of infection were ventilated on the plenum system, and were fitted with apparatus for the aerosol-spray treatment of the air with lactic acid. Air from the special inoculating and grinding cabinets was extracted and passed through an electric furnace on the roof to prevent the discharge of infected particles into the open air. Details are given of the elaborate precautions against infection of the workers ; and among 60 persons employed only three were attacked by the disease. One person was suspected of having inhaled infected droplets while transferring material with a Pasteur pipette ; another had a skin trauma caused by a broken pipette containing infected material ; and the third had been washing unsterilized infected Petri dishes. All three made uneventful recoveries. They and the rest of the staff had been vaccinated.

The scheme was planned on the basis of importation from the U.S.A. of 5,000 cotton rats monthly; this, with local breeding, was expected to provide 12,000 rats monthly. These rates were not attained; altogether 19,223 rats were imported and 10,686 were bred; up to the time of writing 16,882 had been used, but about 20 per cent. were discarded because of death before the fourth day, or insufficient rickettsial yield. During the five and a-half months ending September 30, 201·9 litres of vaccine were prepared.

When the war against Japan came to an end the operation ceased to be urgent, but it was continued till the available rats were used; and by October 31, when 300 litres of vaccine had been prepared, it came to an end.

The preparation of the vaccine was on the lines described in the preceding paper but a few modifications were introduced. The mice used for preparing infecting suspensions were given sulphathiazole in a concentration of 1·0 per cent. in a "cubed diet" instead of by intraperitoneal injection. Smears were stained by alkaline polychromed methylene blue, after heat fixation and treatment with N/1 HCl.

Altogether 15,100 mice were used to prepare the "seed suspensions", but of these 9,163 died or were discarded because of gross contamination. Each batch of vaccine was tested by rickettsial counts and complement-fixation tests; it appeared that the antigenic content was correlated with the rickettsial count, though difficulties were encountered with the staining technique, and probably the true counts were much higher than those actually observed.

Several interesting pieces of research were carried out, including further attempts, with unsatisfactory results, to cultivate the organisms by the yolk-sac method. Filtration experiments suggested that the size of *Rickettsia tsutsugamushi* corresponded closely with that of *R. prowazeki*. Attempts at serial passage through the lungs of sheep and goats failed.

[This brief summary is inadequate to convey a complete impression of a unique "operation" carried out at high pressure because of urgent military necessity. The paper itself is highly condensed and deserves to be read in its original form.] *John W. D. Megaw.*

YELLOW FEVER.

Lairet, F., Jr. La situación de la fiebre amarilla en Venezuela. [**Yellow Fever in Venezuela.**] *Bol. Oficina Sanitaria Panamericana.* 1945, Sept., v. 24, No. 9, 778–83, 3 maps. English summary.

"During 1929 an outbreak of jungle fever occurred in the Cuyuní Valley, a sparsely settled wild region in Venezuela. This proved to be autochthonous, as the settlements where the fever occurred are located at considerable distances from places where, long before, cases had been reported. Since the creation of the National Service for the Prevention of Yellow Fever in Venezuela in 1937, the yellow fever problem has been studied with great care continuously. There are 76 viscerotomy posts in operation, where positive protection tests have been made. This organization has made it possible to locate another yellow fever area, as shown in one of the attached maps. During the 1929 outbreak in Cuyuní, 11 cases occurred among laborers working in sawmills, and other cases were reported in workers clearing timber areas and junglelands where the Haemagogus vector prevails. An *Ateles belzebuth* or "long-sleeve" monkey caught in the San Camilo Forest showed a positive reaction to the disease. In brief, there are in Venezuela two endemic jungle yellow fever areas, both located in the basins of Maracaibo Lake and the

Orinoco River. The first, where the 1944–1945 outbreak centred, lies in the so-called Venezuelan Guiana, bounded by the Caroní river and the borders of the State of Bolívar with Brazil and British Guiana. The second is in the States of Táchira and Barinas, its principal focus being in the so-called San Camilo Forest, on the transitional area between the Andes Mountains and the Apure and Barinas plains. There may perhaps be another yellow fever focus at the northern watershed of the Andes towards Maracaibo Lake, although up to the present time only one case has been reported."

KAPLAN, M. & GLUCK, A. C. Méningo-encéphalite après vaccination anti-amarile. [**Meningo-encephalitis after Vaccination against Yellow Fever.**] *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1945, Nos. 26/31, 374–6.

The record of the clinical symptoms of a 4½-year-old child who became ill 5 days after being vaccinated, by the scarification method, with a neurotropic strain of yellow fever virus supplied by the Pasteur Institute at Dakar. This child developed typical meningeal symptoms about the 11th day after vaccination, with high fever, headache, somnolence, a convulsive crisis and a state bordering on coma. Lumbar puncture produced a clear aseptic fluid and showed a mononuclear hypercytosis. After two or three days there was sudden improvement and the patient made a complete recovery.

Attempts to isolate yellow fever virus from the cerebrospinal fluid by intracerebral inoculation of mice gave inconclusive results, but protection tests with the same fluid were positive. The authors are of the opinion that in order to avoid such accidents it is preferable to use inactive tissue culture virus for vaccination. *E. Hindle.*

DENGUE AND SANDFLY FEVER.

FLORIO, L., STEWART, Mabel O. & MUGRAGE, E. R. **The Etiology of Colorado Tick Fever.** *J. Exper. Med.* 1946, Jan. 1, v. 83, No. 1, 1–10, 6 figs.

The authors, continuing their work on Colorado tick fever [this *Bulletin*, 1945, v. 42, 118], now report experiments on the filterability of the causal agent. Two strains were maintained by passage through hamsters, and serum from infected animals was used as the source of virus in filtration experiments. Hamsters were injected intraperitoneally with test filtrates, and lowering of the white blood count was taken as the criterion of successful infection. Both strains of virus were found to pass through 262 and 181$\mu\mu$ collodion membranes. In seven experiments with filtrates of 24$\mu\mu$ membranes two groups of hamsters showed clear-cut evidence of infection, and the presence of the virus was demonstrated by passage in three other groups. A human volunteer developed Colorado tick fever following subcutaneous injection of infected hamster serum filtered through a 181$\mu\mu$ membrane; similar experiments with the filtrate of a 24$\mu\mu$ membrane proved negative.

The authors conclude that the infectious agent of Colorado tick fever passes through 24$\mu\mu$ membranes and should be classified as a virus.

A. J. Rhodes.

PLAGUE.

GIRARD, G. Hémoculture et bactériémie dans l'infection pesteuse. [**Culture and Bacteraemia in Plague.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 11/12, 328–31.

An original question whether a flea can become infected when fed on a case in which blood culture has proved negative resolves itself for the author into two further questions:—(1) How many organisms in a blood culture are necessary to initiate a plague culture? and (2) Are there any bactericidal or inhibitory substances carried over with the blood in a blood culture which would be sufficient to render non-viable a proportion of the organisms present? The media used, for which the author expresses decided preference, were one in which the peptone was Chapoteaut's peptic peptone, and the other, called "Uclaf", in which the peptone is a tryptic digest of foetal tissue to which gluten is added. In his experiments, using dilutions of a suspension containing about 20 million bacteria per cc., the author arrives at the conclusion that growth of the plague bacillus can be initiated in a suitable medium when the inoculum contains no more than a single living organism. This conclusion seems to provide the answer to the first of the two questions posed. The second question is dealt with firstly by showing that the addition of any blood to any nutrient medium will act favourably in the initiation of growth of the plague bacillus, and secondly by showing that the addition of any blood of any animal, whether a normal animal, an animal which has proved resistant to large testing doses of plague or an animal which has been used to furnish plague serum (antitoxic, not bactericidal) is immaterial so far as relates to any but a favourable effect on the growth of the plague bacillus. And thus the final conclusion may be reached that if a blood culture proves negative it is because that blood contains no viable organisms, and that therefore no flea could become infected by ingestion of that blood. The blood of a plague case, too, contains no bactericidal or inhibitory substances which could complicate growth conditions. *W. F. Harvey.*

CHOLERA.

SOMAN, D. W. & NAIL, S. K. **Sub-Types of Cholera Vibrio isolated from Cholera Patients in Bombay.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 512–14.

A survey of the conditions in town or district during the prevalence of disease has great importance for epidemiology by presenting data for future comparisons and predictions. Such data in India are few, and non-existent in Bombay. The authors have seized the opportunity of epidemic cholera during 1943 and 1945 in Bombay City to obtain, and publish, these data. They refer to the serological sub-types Inaba and Ogawa cholera vibrios, of sub-group I. As the authors mention (and this is one aspect of the value of this Bombay survey)—"Investigations carried out over a period of years in the Madras Presidency have shown extensions and recessions of the area in which the respective sub-types may be the form associated with outbreaks." Their findings given as a summary were: "The prevalent and predominant sub-types of cholera vibrio . . . have been determined . . . . One hundred and sixty-four strains isolated have been tested against cholera O serum group I and Inaba and Ogawa specific sub-type sera. One hundred and sixty-one strains belonged to the Ogawa subtype; the remaining three strains were found to be Inaba sub-type. No 'intermediate' type was recorded . . . ."

W. F. Harvey.

United States Nav. Med. Bull. 1945, Dec., v. 45, No. 6, 1049–53. **Report on Cholera Studies in Calcutta, Value of Chemotherapy in the Treatment of Cholera and use of Blood Plasma in Cholera Collapse. Epidemiology Unit No. 50.** [Amberson, J. M.]

The object of this report is to show the value of chemotherapy in general; it is not an analysis of the relative value of specific medicaments. A comparative series of trials was set up which contrasted no treatment, other than the usual supportive treatment, with chemotherapy, which, of course, involved throughout also the usual supportive treatment. Very special consideration is paid to the use of blood plasma as supportive treatment along with chemotherapy. There was a total of 372 cases of clinical cholera available for analysis.

The groups in this report are set out as: (A) 3 gm. sulphaguanidine every 4 hours for 3 days and twice daily for the next 3 days to a total of 72 gm. (B) Supportive treatment only, represented by intravenous hypertonic and normal saline solution, together with oral stimulants to "offset dehydration emaciation and circulatory failure." This group of patients, the control group, received inert substance (3 gm. calcium carbonate every 4 hours for 3 days). (C) One gm. sulphadiazine every 4 hours for the first day and 2 gm. every 4 hours for the following 2 days to a total of 30 gm. (D) Penicillin intramuscularly in normal salt solution, the initial dose being 100,000 units, with 25,000 units every 4 hours thereafter to a total of 200,000 units. (E) "Received the combined treatments of C and D." Positive value is accorded to chemotherapy and in the matter of data particular stress is laid on the combination of supportive blood plasma with any or all of the chemotherapeutic groups. These data are set out in tabular form:—

	Plasma plus chemotherapy	Chemotherapy alone	Control
Lived	35	274	37
Died	0	3	23
Death Rate	0%	1·1%	38·3%

There can be little doubt of the value of chemotherapy in cholera.

W. F. Harvey.

BACILLARY DYSENTERY.

Smith, L. A. **Shiga Dysentery.** *J. Amer. Med. Ass.* 1946, Jan. 5, v. 130, No. 1, 18–22.

By "Shiga dysentery" the author means that due to any organism of the *Shigella* group; in short, bacillary dysentery. Mild attacks of diarrhoea or of dysentery [referred to by British troops as "the squitters" or "Gyppy tummy"] are known to American troops as "the G.I.s." The early diagnosis of bacillary dysentery on clinical grounds, by microscopical examination of the stools, or by culture of the stools, may be misleading and is often impossible. Proctoscopy in the knee-elbow position is quite easy in a patient with diarrhoea, if performed after a natural motion and without enema clearance. This technique affords the earliest possible positive diagnosis of bacillary dysentery and on repetition shows the progress of the disease. The findings indicate three phases of development of the bowel lesions in bacillary dysentery, *viz.*:—

(1) The *Early Phase* is to be seen within a few hours of the onset of symptoms; the essential features are oedema and generalized hyperaemia, of varying intensity, of the mucosa. There may be miliary mucosal abscesses of pin point to pin head size; initially these are creamy in colour and are due to localized accumulation of leucocytes, later they are topped by shallow ulceration. In severe cases there may be superficial necrosis of the mucosa with the formation of a pseudo-membrane; this, on being stripped off, leaves a red or purple raw surface which bleeds easily.

Efficient early treatment of bacillary dysentery in this stage causes rapid regression of the bowel lesions.

(2) The *Middle Phase* is characterized by granulations, indicative of healing, and by ulceration. The granulations vary in number and size, are dusky red or purple in colour, and are irregular in shape; there may be central ulcers in them. These ulcers are from 0·5 mm. to over 1 cm. in diameter and are round, oval, or serpiginous; their bases are grey and dirty. The proximal surfaces of the valves of Houston are a usual site for these lesions, and a patient with much tenesmus will have many of them in the lower 6 cm. of the bowel. As healing progresses, granulation fills in the ulcers, the colour of the new tissue lightens, and eventually the normal vascular pattern of the mucosa is restored, perhaps many days after the patient is symptom-free.

Efficient treatment of the dysentery at this stage is much more slowly effective in causing regression of the bowel lesions.

(3) The *Late Phase* is seen in severe untreated cases of bacillary dysentery where indolent ulceration persists for long and heals slowly, often with extensive superficial scarring.

After discussing the differential diagnosis of bacillary dysentery, and reaffirming that in 90 per cent. of cases early proctoscopy yields the diagnosis, the author reviews the response to treatment of his cases, symptomatically, objectively, and in relation to the reversal of the cultural findings in the stools. Previously, clinical response and the time taken to obtain it have been the criteria of success of treatment; but these are misleading unless proctoscopic examinations are made. Four groups of cases were treated respectively:—(1) without chemotherapy; (2) with sulphaguanidine—4 gm. three-hourly for four doses, and then 2 gm. four-hourly—a total of 46 gm. in 72 hours; (3) with sulphadiazine (given with equal weights of sodium bicarbonate) 4 gm. initially, then 2 gm. four-hourly for four doses, then 1 gm. four-hourly for four doses, and then 1 gm. six-hourly for seven doses—a total of 23 gm. in 72 hours, and (4) by combined sulphaguanidine and sulphadiazine therapy (sulphadiazine as outlined for three days; on the third day, sulphaguanidine as outlined, this being continued until the fifth day).

The author concludes that the best period for effective treatment is in the first twenty-four hours of the disease. Sulphadiazine at this time causes prompt cessation of the symptoms and signs, but the mucosal lesions may not disappear until some time after this, especially if treatment has been delayed. Sulphadiazine appeared to be more rapid in its action than sulphaguanidine, and caused the stools to become negative on culture within 24 to 36 hours.

A. R. D. Adams.

Majumder, A. R., Bagchi, A. K. & Ghosh, B. K. **Sulphanilyl Benzamide in the Treatment of Bacillary Dysentery. (A Preliminary Note.)** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 500–501.

Sulphanilyl benzamide was tried in 19 cases of bacillary dysentery; cultures had been made in 14 of the cases but in only 4 were pathological organisms isolated—Sonne in 3 and Flexner in 1. The dosage was: "2 tablets three

times a day for the first few days and later twice a day; the length of the treatment varied between 4 and 7 days according to the time when the stool became normal." The concentration of the drug in the blood was estimated in 7 cases, the total amount varying from 2·94 to 12·50 mgm. per 100 cc. and the amount of free drug from 2·2 to 10 mgm. per 100 cc. The average number of days for a clinical cure was 4·6. Two patients died and the other 17 recovered. No toxic effects were produced by the drug. [See also this *Bulletin*, 1942, v. 39, 35; 1945, v. 42, 207; *Bulletin of Hygiene*, 1945, v. 20, 391.] *J. F. Corson.*

AMOEBIASIS AND INTESTINAL PROTOZOAL INFECTIONS.

Ferreira, Fernando da Cruz & Egrejas, Gustavo. As protozooses intestinais em Cabo Verde. [**Intestinal Protozoal Infections in Cape Verde.**] *Supplement No. 1 to An. Inst. Med. Trop.* Lisbon. 1945, Aug., 103 pp., 10 figs. & 5 pls. [Bibliography.]

This publication, from the Institute of Tropical Medicine of Lisbon, has to do with the intestinal protozoa of the Cape Verde Islands as exemplified by the results of the examination during 1942 and 1943 of 555 faecal specimens from patients in the hospital of St. Vincent. The results were: *E. coli* 142, *E. histolytica* 56, *E. nana* 13, *I. bütschlii* 4, *G. intestinalis* 26, *C. mesnili* 14, *T. hominis* and *E. hominis* (*Embadomonas intestinalis*) 11. On the basis of these results this long treatise of upwards of 100 pages has been written. The information given is of local interest but it is doubtful if it contains anything new for the general reader. *C. M. Wenyon.*

Lamy, L. Action du para-aminophénylsulfamide (1162F) sur les cultures d'amibes. (Note préliminaire.) [**Action of Para-aminophenylsulphamide on Cultures of Amoebae.**] *Ann. Inst. Pasteur.* 1944, Sept.–Oct., v. 70, Nos. 9–10, 318–20.

Working with cultures of *E. histolytica* and *E. invadens* the author has noted, as others have done, that frequent subcultures are necessary, owing to the rapid development of the bacteria which after a few days bring development of the entamoebae to an end, and finally kill them in, at most, fifteen days. It occurred to him that if the bacterial development could be checked the entamoebae might continue to develop for longer periods. It was found that the addition of para-aminophenylsulphamide (1162F) to the medium (coagulated horse serum, Ringer serum, rice starch) in a concentration of 0·5 per cent. had the desired effect of checking the bacterial growth without injuring the entamoebae, which continued to develop satisfactorily for one or two months. It is thus possible to extend considerably the intervals between successive subcultures. *C. M. Wenyon.*

Adamson, D. H. **The Incidence and Diagnosis of Amoebic Dysentery in the 2nd N.Z. Expeditionary Force.** *New Zealand Med. J.* 1945, Dec., v. 44, No. 244, 323–7.

In the Middle East the number of suspected cases of amoebic dysentery was not unduly large; in Italy it was considerable. In both areas parasites were not always recovered from patients with a suggestive clinical history and symptoms. A description is given of the vigorous purgation deemed necessary to obtain the repeated stools regarded as essential for a successful microscopical

diagnosis, and of the elaborate technique followed in their examination. The statement is made that, with this technique, " no more than four patients' purgative specimens can be coped with by one worker during the morning." (At least six specimens from each case are expected within the time of observation.) Microscopical diagnosis was seemingly confined to the recognition of the amoebic trophozoites in " purgative specimens " as " it was not found possible to differentiate with certainty cysts of *E. histolytica* from those of other amoebae." *A. R. D. Adams.*

HALL, B. & BILLINGS, J. J. **Amoebiasis in New Guinea, 1943–1944.** *Med. J. Australia*, 1945, Dec. 8, v. 2, No. 23, 393–8.

The authors comment on the frequency of amoebiasis in Australian troops and ex-service personnel during and after service in New Guinea and in the Middle East. They refer to the possible acquirement of the infection from such cases by Australian civilians living in association with them under insanitary conditions. After a brief history of amoebiasis in New Guinea, an account is given of the infection, its complications, diagnosis and treatment, in troops there during the course of the recent war. This account contains nothing original. *A. R. D. Adams.*

BÖE, J. **Complement Fixation Antigen in** *Entamoeba histolytica* **Infection.** *Proc. Soc. Exper. Biol. & Med.* 1945, Oct., v. 60, No. 1, 31–3. [10 refs.]

The author describes the preparation of a simple antigen for complement fixation tests for *E. histolytica* infection. It was prepared by centrifuging, at low speed, cultures of *E. histolytica* from ten tubes of a modified Cleveland-Collier medium. The deposit was taken up in saline and re-centrifuged. This was repeated eight to ten times till the supernatant fluid was clear. The deposit, consisting chiefly of amoebae with traces of starch and a few bacteria, was thoroughly dried and powdered and stored in sealed ampoules. For use, the powder was suspended in saline and titrated for its anticomplementary dose, one-fourth of which was used in the actual test carried out according to the usual Wassermann technique. As a control to the sera under test, serum from a rabbit immunized with the antigen was used. This was strongly positive. Furthermore, as an additional control, antigen prepared by Craig's alcohol method was used in parallel tests. Sera from 121 Norwegians, five of whom were carriers of *E. histolytica*, were subjected to test. Only two of the sera gave a positive result, and this with both antigens. One was serum from one of the five carriers, the other was from one of the individuals in whom amoebae could not be detected after numerous examinations. The latter, however, suffered from some obscure liver condition. In a previous paper the author records the results of the examination for *E. histolytica* and other intestinal protozoa of a group of 1,111 individuals in Norway [this *Bulletin*, 1944, v. 41, 572]. *C. M. Wenyon.*

DE SILVA, S. **Significant Observations on Amoebic Hepatitis. A Clinical Review of 200 Patients.** *J. Trop. Med. & Hyg.* 1945, Dec.–1946, Jan., v. 48, No. 6, 152–7, 3 charts.

The author states that the incidence of amoebic hepatitis in Ceylon has recently increased ; in 1929 there were 88, and in the first ten months of 1945 1,279 cases of the condition diagnosed in the General Hospital, Colombo.

He records a number of general impressions on some 200 of these cases, and states he is " obliged to avoid details owing to lack of information " ; these impressions contain none that can be considered original. *A. R. D. Adams.*

Reddy, D. G. & Rangam, C. M. **Jaundice in Amoebic Liver Abscess. A Report of Two Cases.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 501–2, 4 figs. on 1 pl.

Two cases of amoebic abscess of the liver, diagnosed at post-mortem examination, are described; in one case a single abscess had ruptured into the peritoneal cavity, while in the other case there were three abscesses in the right lobe of the liver, but none had ruptured, though a diffuse peritonitis was present. Amoebae were found in the walls of the abscesses in both cases. Both patients were jaundiced; in one case the abscess pressed on the right hepatic duct while in the other case the common bile duct was blocked. *J. F. Corson.*

Gilje, L. E. & Lampson, R. S. **Acute Appendicitis in Amebic Dysentery. Report of a Case.** *U.S. Nav. Med. Bull.* 1946, Jan., v. 46, No. 1, 109–11.

Knoll, Elta W. & Howell, Katharine M. **Studies on *Dientamoeba fragilis*: its Incidence and possible Pathogenicity.** *Amer. J. Clin. Path.* 1945, May, v. 15, No. 5, 178–83. [19 refs.]

In discussing *Dientamoeba fragilis*, the authors note that the various surveys in which it has been identified indicate that its distribution is widespread throughout the world. If laboratory workers were experienced in the identification of this parasite they would find that its incidence in any population is probably as high as or even higher than that of *E. histolytica*. As regards its possible pathogenicity, a series of cases is described in children and adults in which it appeared to be the only organism present, apart from non-pathogenic bacteria. The symptoms in these cases were abdominal discomfort and pain, bouts of diarrhoea, nausea and vomiting and some fever. During the attacks *D. fragilis* in very large numbers appeared in the stools. In some of the cases symptoms had persisted for two or more years. In all these cases the symptoms ceased under carbarsone therapy, while *D. fragilis* disappeared from the stools. As a result of their studies the authors conclude that *D. fragilis* can be pathogenic to man. Attempts to discover the organism in dogs, cats and rats met with no success, while repeated administration of rich cultures to kittens *per os* and *per rectum* failed to bring about an infection. *C. M. Wenyon.*

Díaz Atiles, A. **A Study of Balantidiasis coli. Report of Two Cases in Children successfully treated with Stovarsol.** *Puerto Rico J. Pub. Health & Trop. Med.* 1943, Mar., v. 18, No. 3, 287–99. [Refs. in footnotes.] [Spanish version 300–313.]

The author, in reviewing recent literature, gives an account of two cases of *Balantidium coli* infection in boys nine years of age, both of whom had been in intimate contact with pigs. The persistence of the infection for six weeks was established by repeated stool examinations before treatment with stovarsol was instituted. In one case response to treatment was immediate, the stools being negative after 48 hours, but treatment was continued for a week. In the other case there was no response for three weeks. With increased dosage (750 mgm. daily) the stools became consistently negative. In both cases, a year after cessation of treatment, the stools were still negative. Two other children are referred to; they were associates of the others, but treatment was not carried out as the infection, from which they both suffered, was only of a transient nature. *C. M. Wenyon.*

HUMPHREY, A. A. *Isospora hominis* **Infection in Man.** *J. Amer. Med. Ass.* 1946, Jan. 19, v. 130, No. 3, 143–5, 1 fig.

Three cases of *Isospora hominis* infection are described in men who had served in Okinawa and were evacuated to Guam for hospital treatment in July 1945. All three suffered from abdominal discomfort or diarrhoea. The longest period during which oöcysts were observed in the stools was during 15 days hospitalization. In all three cases there was some degree of eosinophilia.

C. M. Wenyon.

RELAPSING FEVER AND OTHER SPIROCHAETOSES.

GREAVES, F. C., GEZON, H. M. & ALSTON, W. F. **Studies on Louse-Borne Relapsing Fever in Tunisia.** *U.S. Nav. Med. Bull.* 1945, Dec., v. 45, No. 6, 1029–48, 9 figs. [49 refs.]

A general account with special reference to the treatment and control of louse-borne relapsing fever, due to *Spirochaeta berbera*, in Tunisia.

Since the outbreak of 164 cases in Tunis during 1912 there were only sporadic cases until July 1943, when a major epidemic began which was still in progress during 1945. In 1943 only 6 cases were recorded, but in 1944 the monthly cases rose from 8 in January to 4,451 in December, and continued to rise in 1945 to 6,536 in March. The total for 1944 was 18,534, and for the first 4 months of 1945 reached 23,221 cases. These statistics are considered by the public health authorities to involve only one-fifth of the actual numbers, for the majority of the Arab population seem to prefer not to attend for medical treatment.

The mortality rate showed marked differences. In one small village 80 untreated cases had a mortality rate of 1·25 per cent., whilst in another very similar village 71 untreated cases showed a rate of 46·5 per cent.; among 3,806 cases treated in the Ernest Conseil Hospital in Tunis, the rate was 5·46 per cent. There is no satisfactory explanation for these differences, and it is possible that other diseases, such as typhus, typhoid, or plague, may have complicated the relapsing fever.

The clinical symptoms were typical, but 10 per cent. of 112 untreated cases had no relapses, 62·5 per cent. showed only one relapse, and 22·3 per cent. two relapses, whilst occasional cases showed three, four or five relapses. Laboratory studies were made on 40 patients. The most constant finding was a complete absence of eosinophils in all patients, even after the clinical termination of illness.

Penicillin was used for the treatment of 27 patients, the total dose being 480,000 units for adults and 360,000 for children. In most cases the spirochaetes disappeared within 24 hours and none was ever found after 48 hours. All these patients showed a rapid clinical recovery, and none had a relapse. The results with neoarsphenamine were also equally satisfactory, and since this is cheaper and easier to administer it is the drug of choice, except when relapsing fever is accompanied by jaundice.

Three guineapigs and 27 mice were inoculated with infective material, but only in the case of one guineapig and 21 mice receiving large doses of heavily infected blood were spirochaetes recovered, and then only in the first 24 hours. It is evident that these animals are unsuitable for the isolation of this spirochaete directly from human blood.

Experiments were made on the control of the epidemic in an isolated Arab village by the use of 10 per cent. DDT, applied by dusting each member of the

household and the bedding and extra clothing. The disease completely disappeared within a fortnight after this treatment, and neither lice nor nits were found on 75 people examined in the village 10 days later. Another experiment was made in Ferryville. In the treated area 76·7 per cent. of 851 persons were dusted with DDT : in the adjoining control area there were 1,436 persons. The results are shown in the following table :—

Incidence of relapsing fever in the Bellevue quarter of Ferryville, May 1945.

		Total	No. deloused	Percent. deloused	No. huts	No. sick	Percent. sick	No. with Positive Blood Smears
May 5–12	DDT	851	653	76·7	147	46	5·41	14
	Control	1,436	none	0·0	129	47	3·27	12
May 17–19	DDT					2	0·23	1
	Control					41	2·85	12
May 26–28	DDT					4	0·48	1
	Control					24	1·67	8

It would seem, therefore, that one application of 10 per cent. DDT powder, if thoroughly applied to a population, is almost completely effective in stopping a louse-borne epidemic of relapsing fever. *E. Hindle.*

Lofgren, Ruth & Soule, M. H. **The Structure of *Spirochaeta novyi* as revealed by the Electron Microscope.** *J. Bacteriology.* 1945, Dec., v. 50, No. 6, 679–90, 6 figs.

Richardson, A. P., Walker, H. A., Loeb, Prudence & Miller, I. **The Experimental Basis for the Quantitative Chemotherapy of *B. novyi* in Mice with a Comparison of Action of Penicillin and Dichlorphenarsine Hydrochloride.** *J. Pharm. & Exper. Therap.* 1945, Sept., v. 85, No. 1, 23–35, 2 figs. [10 refs.]

The authors describe detailed experimental procedures for quantitative chemotherapeutic experiments with mice infected with *Spirochaeta novyi*. They first show that the number of spirochaetes injected has a considerable effect on the course of untreated infections. Also that the degree of anaemia which develops is roughly proportional to the number of organisms in the peripheral blood.

Five samples of penicillin were tested for their action on the spirochaetes, *viz.* : crystalline sodium penicillin G. ; commercial sodium penicillin Squibb ; pilot plant lot No. 860, containing almost no penicillin G ; commercial calcium penicillin Squibb, probably a mixture of G and other penicillins ; and methyl ester of penicillin G. The activity of these five compounds was compared with dichlorphenarsine hydrochloride in three types of experiments, *viz.*, frequent subcutaneous injections, single daily injections, or given by mouth. On the basis of Oxford units, no significant differences were found between the first four samples of penicillin irrespective of the method of administration. The methyl ester of penicillin G was found to be equal to free penicillin G when injected, but had less than one-twentieth of that activity when given orally.

When administered by frequent subcutaneous injections, dichlorphenarsine hydrochloride is, weight for weight, equal to crystalline sodium penicillin G in its activity against *Spirochaeta novyi*. *E. Hindle.*

NÁJERA ANGULO, L. Receptividad de los murciélagos cavernicolas españoles. (*Miniopterus schreibersii, Myotis myotis, Rhinolophus euryale* y *Rh. hipposideros minimus*) al virus de la fiebre recurrente mediterránea. [**The Susceptibility of Spanish Cave-dwelling Bats to the Spirochaete of Mediterranean Relapsing Fever.**] Reprinted from *Bol. de la Real Soc. Española Hist. Nat.* Madrid. 1945, v. 43, 217–28, 1 map.

The relationship between *Spirochaeta hispanica* and the spirochaetes causing relapsing fever in Portugal and in Greece (*Sp. hispanica* var. *peloponnesica* of Caminopetros) is of considerable interest ; the author calls the fever caused by these organisms Mediterranean relapsing fever. As biological reactions are important aids in the identification of spirochaetes of apparently identical morphology, he made experiments in 1939 to test the susceptibility of some cave-dwelling bats to infection with *Sp. hispanica*.

These bats were difficult to keep alive and it was found best to keep them at a temperature of 18°C. and in an atmosphere of a humidity approaching saturation ; to get a short incubation period they were inoculated intraperitoneally with blood of guineapigs heavily infected with *Sp. hispanica*, and those which survived for 4 days or more were examined post mortem.

The results are shown in notes and tables : four species were found susceptible namely, *Miniopterus schreibersii, Myotis myotis, Rhinolophus euryale*, and *Rhinolophus hipposideros minimus*. One of these bats, *M. myotis*, is a host of *Schizotrypanum vespertilionis*. *J. F. Corson.*

YAKOUB, K. **Relapsing Fever in Egypt.** *J. Roy. Egyptian Med. Ass.* 1945, July, v. 28, No. 7, 327–30.

TAFT, W. C. & PIKE, J. B. **Relapsing Fever. Report of a Sporadic Outbreak, including Treatment with Penicillin.** *J. Amer. Med. Ass.* 1945, Dec. 8, v. 129, No. 15, 1002–5.

A study of eleven cases of relapsing fever observed and treated at an army hospital in Texas during August and September 1944 and April and May 1945. All the patients, shortly before admission, had camped in a bivouac area where many *Ornithodorus turicata* were present ; later it was shown that spirochaetal infection was present in the ticks.

The clinical diagnosis of the disease in the initial stages was found to be difficult ; it was established by dark field examination or stained smear of the peripheral blood. Spirochaetes were found in the blood only during the febrile period when the temperature was above 102°F. Five of the patients developed a skin eruption having the appearance of erythema multiforme, which persisted for 24 to 48 hours. A biopsy was made of one of these skin lesions and spirochaetes were found in the superficial layers of the dermis, even during the afebrile period. [This interesting observation seems to be the first record of relapsing fever spirochaetes being found in this site.]

Significant neurological manifestations developed in five of the patients, even suggesting a diagnosis of meningitis. Spirochaetes were never found in the spinal fluid, however, either by direct examination or mouse inoculation. Treatment with oxophenarsine hydrochloride administered intravenously with or without bismuth, gave disappointing results, for although it shortened the attack it did not prevent relapses. In two patients penicillin was given—40,000 units every three hours for 60 doses, a total of 2,400,000 units. Both

were afebrile within 72 hours and showed no relapses. All the patients recovered without any serious complications incident to the disease or to the penicillin treatment. *E. Hindle.*

HYND, R. S. **The Construction of Army Huts to limit Infestation by** *Ornithodoros moubata* **(Relapsing Fever Tick).** *East African Med. J.* 1945, Oct., v. 22, No. 10, 337–42, 2 figs.

To investigate the possibility of constructing a tick-proof hut, a series of experiments were conducted with *Ornithodorus moubata* to discover the climbing powers of the tick, the conditions necessary to make the tick leave the floor to climb, and if projecting metal strips in walls would act as barriers to climbing ticks.

The experiments were carried out in a specially designed wooden box fitted inside with two projecting metal strips to act as obstructions to ticks attempting to climb up the sides. A glass observation panel was provided in one side. A second box to hold a guineapig was fitted into the top of the first. The experiments are described, and from the results the author concludes that, in lightly infested huts, there is little urge for ticks to climb the walls ; they will do so in heavily infested huts and in those with impermeable floors in order to find cracks ; the climbing urge is not influenced by the presence of a living being ; metal strips (rough or smooth) set into the walls and projecting from them do act as barriers.

Therefore he makes the following suggestions ; earth floors should be avoided as they are the normal habitat of *Ornithodorus moubata* ; a hard floor, free from cracks, can be made of bitumen, concrete, or beaten tar-and-earth ; it should be six inches thick and should have a metal strip inserted midway through its thickness and projecting three inches outwards all round. This will not, of course, prevent ticks being carried into the hut on the feet and clothing. A foot or so above the floor another metal strip should be inserted into the walls and this should protrude three inches, all round the hut, both inside and outside.

It is hoped that a test on a full scale model can be arranged, for if successful " the decrease in the incidence of relapsing fever which could be expected if all huts were constructed in this manner might well be worth the additional expense involved in construction." *H. S. Leeson.*

YAWS AND SYPHILIS.

DUVALIER, F. Contribution à l'étude du pian en Haiti. L'aspect médico-social et l'oeuvre de la Mission Sanitaire Américaine. [**Contribution to the Study of Yaws in Haiti. The Medico-social Aspect and the Work of the American Sanitary Commission.**] Reprinted from *Bull. Assoc. Méd. de Langue Française de l'Amérique du Nord-L'Union Médicale du Canada.* 1945, June, v. 74, 20 pp., 3 figs., 1 map & 1 chart. [37 refs.]

Ninety per cent. of the Haitians are illiterate, and 80 per cent. of the rural population are infected with yaws. Hygienic conditions are very poor, and nutrition is defective. The inter-relationship of ill-health and low economic output is stressed. Yaws is particularly prevalent in the mountainous rural areas, where difficulty of access is a hindrance to effective treatment. Cases secondary and tertiary, were more numerous during the rainy seasons.

The author thinks that yaws was endemic before Columbus landed, and also that it was spread through the Slave Traffic. During the American occupation,

1915–1924, anti-yaws work was carried out, and rural dispensaries were opened, but from 1931 to 1942 this activity practically ceased. In 1943 a further campaign was started by the American Sanitary Mission, but it was considered that treatment alone was not sufficient, and that an approach should be made along the lines of social medicine. Anti-yaws centres were opened. Mapharsen (3 intravenous injections of 0·6 [presumably a misprint for 0·06 gm.] at 8-day intervals), sulpharsphenamine and bismuth salicylate (3 intramuscular injections of 1·0 cc. [concentration not stated] at 8-day intervals) were used. The results with mapharsen were " rather encouraging."

Although the social aspect is stressed the isolation and illiteracy of the population offer a tremendous barrier to any rapid achievement.

Any plan for the eradication of yaws in Haiti should comprise a rational organization of the rural area, with construction of new roads and repair of existing ones, the establishment of a normal standard of living for the natives, and the education of the 90 per cent. illiterate population which seems hardly to have emerged from slavery. *C. J. Hackett.*

MONTEL, R. Contribution à l'histo-pathologie de la lésion primaire d'inoculation et des lésions secondaires du pian. Chancre pianique, pianides, pianomes. [**The Histopathology of the Primary and Secondary Lesions of Yaws.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 3/4, 71–84, 8 figs. on 4 pls. & 1 text fig. [23 refs.]

The author described in 1928 the primary lesion of yaws and contrasted it with the corresponding lesion of syphilis [see this *Bulletin*, 1929, v. 26, 951]. He later pointed out that, contrary to the general view, secondary lesions were not merely " disseminated primary lesions " but distinct. In the present article he takes up this question again. He has studied minutely the microscopic anatomy and histology of 6 primary yaws chancres, 2 secondary rashes and 5 pianomas (generalized lesions), and he describes the histology of twelve of these in great detail. The contribution is illustrated by excellent photomicrographs depicting the changes which he describes. Those interested should consult the original ; the description is very condensed and to convey the details to readers would entail almost a *verbatim* transcription. As described in the letterpress the histological differences are quite marked. Briefly, the primary yaw is characterized by ulceration which destroys the upper layers of the skin and presents at the border a marked hyperacanthosis with depigmentation. One photograph shows this clearly. The epidermis is invaded by motile cells in tracks and small groups, displaced by oedematous areas. Beneath this, migratory cells densely infiltrate with a conglomeration of polymorphonuclear cells, plasmocytes, lymphocytes, histiocytes and many eosinophiles, and in the deeper parts of the dermis is a certain degree of sclerosis. Giant cells are never present.

In the second group of lesions, the pianides, the epidermis is thickened, but there is no hyperacanthosis, the migratory cells penetrate at isolated spots only. Infiltration is not marked and is situated mostly round the cutaneous vessels and hair follicles, and is made up of lymphocytes and histiocytes, rarely any polymorphonuclears. Plasmocytes are absent. In the pianoma, which is a papilloma without ulceration, the hyperacanthosis of the epidermis is great ; the crust is stuffed with migratory cells which have traversed the infiltrated epidermal layers. A thick plasmocytic barrage is present ; the vessels are congested, new capillaries formed, stuffed with eosinophiles and swollen endothelial cells. There are no giant cells and no sclerosis of the deeper dermal layers.

The rest of the article is taken up in stressing, with quotations from the literature, the tendency on the part of those working on the pathology of yaws to confuse these changes, and it ends with a brief statement of certain differences

which distinguish yaws lesions from those of syphilis, namely that the yaws lesions tend to be dermotropic, that the infiltration is largely limited to the subpapillary layer, vascular lesions are slight, infiltration is not nodular and perivascular and the deep vessels are not affected. There are others, but these are the chief. *H. Harold Scott.*

MONTEL, R. Les accidents secondaires cutanés du pian : roséole, pianides, pianomes. [**Secondary Rashes in Yaws.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 5/6, 137–45, 5 figs. (4 on 2 pls.). [15 refs.]

In the author's view too little attention has been paid to some of the cutaneous manifestations of yaws, and the inexperienced are apt to regard them as new conditions and to give them a variety of names. He describes secondary lesions of the skin under four groups: (1) *Roseola*, fleeting and therefore often unnoticed, and hence not mentioned by some and denied by others. It appears most commonly about 20 days after the primary sore. (2) *Pianides*, appearing in the interval between the roseola and the generalized eruption (which he calls pianomas). They always precede the general eruption but may continue to coexist with it. He speaks of four kinds of pianides: (i) Furfuraceous, circinate, lichenoid or like pityriasis ; at one stage the condition resembles cutis anserina. The lesions are usually on the trunk, and cause considerable itching. (ii) Papular, isolated or agminated papules, in size from that of a lentil to that of a large pea, buff- or copper-coloured. They also cause itching, but usually regress spontaneously. (iii) Circular areas of desquamation, erythematous and papulo-squamous, on the palms and soles, 1–2 cm. in diameter ; by fusion they may form curious geometric figures. (iv) Plantar hyperkeratosis, often serpiginous and presenting a worm-eaten appearance. (3) *Mucosal lesions* on the lips and tongue, in plaques resembling those of syphilitic leucoplakia, with well-defined border, sometimes whitish or pearly or greyish yellow, mammillated ; they may ulcerate. (4) *Pianomas*, or vegetating papillomatous lesions, oozing, but not desquamating. Of these also the author distinguishes four forms : (i) Developing from the original yaw ; (ii) Resulting from transformation of one of his group 2, pianides ; (iii) The generalized yaws eruption ; (iv) The confluent condylomatous yaws.

Although these are all detailed as distinct, they do not always remain so, and one may pass into another ; the papular pianide (2 (ii) above) may become a " papillomatous pianoma " (4 (i) above), and the eruptive pianoma (4 (iii)) may become a vesicular papule or pustule (2 (ii)), but the author thinks it well to point out these various forms in order that their histopathology may be more closely studied. The article is well illustrated.

H. Harold Scott.

WHITEHILL, R. & AUSTRIAN, R. **Further Observation on the Treatment of Yaws with Penicillin.** *Bull. Johns Hopkins Hosp.* 1945, June, v. 76, No. 6, 274–94, 10 figs.

Forty-one Fijian cases of primary and secondary yaws, in which spirochaetes were found and the Kahn test was positive, are reported. The infections had been present 1–12 months and severe, moderate and mild cases were about equal in numbers. Only eight patients had received any previous specific treatment, the maximum being " five injections of arsenic " 9 months previously. Thirty of the patients were under fifteen years of age. Penicillin was given intramuscularly in doses of 15,000 to 30,000 units at intervals of 3–4 hours, to total dosages of 100,000 to 2,400,000 units.

In all cases except three no spirochaetes were found 16 hours after treatment had started, and in those three no spirochaetes were found after 24 hours. No Herxheimer reactions occurred. In 37 cases healing was complete in three weeks, despite differences in total dosage. In the other four cases the healing of single lesions about the ankle caused the delay. [Perhaps some other cause was present in all these cases ; tinea imbricata was present in one of them.]

The longest period of follow-up was 20 weeks (two cases) ; only 14 patients were observed for more than 10 weeks. In no case was a positive Kahn reaction permanently reversed, but no case receiving more than 1,200,000 units was observed for longer than 10 weeks. One clinical relapse after 280,000 units was observed nine weeks after admission.

The use of 100,000 units in four doses in 9–12 hours is probably as effective as many incomplete courses of arsenicals given over a longer period. It will cause the healing of secondary lesions, and thus render the patient non-infectious, at least for the time being. Further follow-up work is being carried out at the Colonial War Memorial Hospital at Suva.

One case of tertiary yaws of five years' duration in a child aged fifteen is reported. The skin and bone lesions responded more slowly, but they had previously not healed despite prolonged and repeated arsenical and bismuth treatment. *C. J. Hackett.*

Guimarães, F. N. Penicilina pela boca. Demonstração de sua atividade pela cura clinica da bouba. (Nota prévia). [**The Curative Action in Yaws of Penicillin taken by Mouth.**] *Hospital.* Rio de Janeiro. 1945, Aug., v. 28, No. 2, 229–32, 2 figs. English summary.

" Demonstration of the activity of Penicillin by mouth, was obtained by the clinical cure of three cases of yaws, with primary and secondary lesions.

" The Wassermann reactions were negative in two cases, after a month of observation, but returned positive.

" The treatment consisted in 1,000 O. u. by mouth, diluted in water, each two hours (excepted at 24 and 2 o'clock), during 10 days.

" The total amount of Penicillin per patient was 100,000 Oxford units."

LEPROSY.

Revista Brasileira de Leprologia. S. Paulo. 1945, Sept., v. 13, No. 3, 133–227.

The *Revista de Leprologia* in 1938 put forward the basis of a new clinical classification of cases of leprosy. In 1945, mainly at the instance of Dr. Lauro de Sousa Lima, doubts began to be expressed on the satisfactoriness of that classification, and in view of the Pan-American Congress of Leprologists which is to be held in Rio de Janeiro in 1946 the present is looked upon as a suitable time to reconsider the classification of cases of this disease.

This number of the *Revista* is devoted entirely to the subject. It opens with a reproduction of Dr. Lauro de Sousa Lima's paper in which he stated that, on the whole, the South-American classification is satisfactory, but that there are certain points needing amplification or clarification, in particular the difficulties in classifying the non-characteristic forms and those cases which undergo changes of type, and intermediate relapsing cases. Examples are given where there is a conflict between the different factors of criteria in classification.

Thus : (1) Cases clinically and histologically of the tuberculoid form, but

bacterially negative and with negative lepromin reaction. (2) Cases clinically and histologically tuberculoid, bacterially positive but lepromin negative. (3) Clinically not characteristic, but histologically lepromatous. (4) Clinically not characteristic, but histologically tuberculoid. (5) Those with tuberculoid nerve lesions, lepromin negative.

The whole question has been referred to bodies which deal with leprosy and to individual specialists who have given their working lives to study of the disease for expression of their opinions on six main points :—

1. Should the results of the Mitsuda reaction be discarded as a basic criterion for clinical classification or should the test be retained until further studies have proved its value and significance ?
2. Should the existing ideas on the results of search for the organism be altered ?
3. How should the " uncharacteristic forms " be designated ?
4. On what points should stress be laid in classifying the nervous sub-types ?
5. Should the phenomena of change of form, which the majority of cases undergo, be included or excluded as a basis in separating the fundamental types ?
6. How ought the intermediate or the relapse lesions to be classified ? Under the tuberculoid form or the lepromatous form, or should they be placed apart in a new group ?

These six questions were debated by the Rio de Janeiro Commission, by that of São Paulo, by the Argentine Commission (three views are expressed in separately contributed papers by members of this body) and the Commission of Minas Gerais.

It is not possible to detail the varying conclusions of the different bodies of men and of individual specialists ; for examples, Dr. Paulo Rath de Sousa, a pathologist, divides the cutaneous forms alone of leprosy into 15 types, four of the lepromatous, seven of the non-characteristic and four of the tuberculoid. For this information readers must consult the original. They will find it of considerable interest, though we fear that the majority will " come out by the same door wherein they went." *H. Harold Scott.*

Arnold, H. L., Jr. & Tilden, I. L. **The Classification and Nomenclature of Leprosy with Suggestions for a Simplification of Both.** *Ann. Intern. Med.* 1945, July, v. 23, No. 1, 65–73. [16 refs.]

The authors point out that leprologists and dermatologists differ in their nomenclatures of leprosy, and they discuss the classification of the Manila and Cairo Conferences. They particularly object to the term " mixed leprosy " on the ground that in nearly all cases both the nerves and the skin are affected, and they also consider that the terms " neural leprosy," " macule " and " nodule " are misleading. The essential difference is between the mild infections of the superficial nerves and the skin, with very scanty leprosy bacilli, and the severe lepromatous forms, with abundant bacilli in the lesions of thickened skin and nerve trunks. They therefore suggest a classification into only lepromatous leprosy and tuberculoid leprosy, the latter including the " neural " forms. *L. Rogers.*

Dharmendra. **Leprosy in Bengal.** *Leprosy in India.* 1945, Oct., v. 17, No. 4, 109–15, 1 map.

The humid province of Bengal has a high leprosy rate ; the number of cases is now estimated at from 200,000 to 300,000, as compared with a total of about 21,000 cases returned by the 1931 census. The district rates are highest in the western area (1 to 3 per cent.), in the central and northern districts moderate rates (0·5 to 0·9 per cent.) are found, and the lowest rates (below 0·5 per cent.)

occur in the low-lying delta districts of South-East Bengal ; this incidence is illustrated by a map. The total infective cases are estimated at 50,000 to 60,000, but the 7 indoor institutions accommodate only 786, many of whom are uninfective nerve cases. The very important and costly isolation of infective cases is therefore totally inadequate ; it should be greatly increased. There are also about 150 out-patients' clinics in the province, at which about 20,000 cases are treated yearly. These clinics also need to be increased greatly, and where they are not available arrangements should be made for the treatment of leprosy patients at the Government and District Board hospitals and dispensaries, as has been done in the Madras Province. Homes are also required for uninfective, crippled patients. *L. Rogers.*

Hasseltine, H. E. **History of Leprosy in the New England States.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 67–78, 4 figs. on 1 pl. [13 refs.]

Faget, G. H. **Leprosy in Military Service.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 65–6.

Doull, J. A., Guinto, R. C., Rodriguez, J. N. & Bancroft, Huldah. **Risk of Attack in Leprosy in relation to Age at Exposure.** *Amer. J. Trop. Med.* 1945, Sept., v. 25, No. 5, 435–9.

In this paper the data collected during a house-to-house survey in two similarly situated municipalities in the Cebu Island, Philippines, are analysed in relation to age at the time of exposure to house infection from a lepromatous case of the disease. The duration of the exposure was noted in each case and each year was taken as a unit to determine the incidence rate of new infections per 1000, person-years. The average annual incidence of infections was 4·6 per 1,000 person-years ; this is five and a half times the rate for persons in the general population not known to have been subject to household exposure. The data are tabulated and analysed in accordance with the ages at which infections took place and also for sex, with instructive results. Among children first exposed when under 5 years of age, but mostly exposed from birth, no cases were found under the age of five years, but the highest incidence is reached about 10 years after exposure. The maximum incidence rate of 17·8 per 1,000 occurred in those exposed to infection below the age of five, and aged 10 to 14 years at the time of attack, but the rate fell off again to 12·4 at 15 to 19 years of age and to 3·5 for those over 20 years old. The average interval between exposure to infection before the age of 10 years and recognition of the disease in 64 persons was 10·5 years, but in 25 persons first exposed after the age of 10 years it was only 6 years. The average annual incidence rate for those exposed to infection falls steadily from 7·6 per 1,000 for those exposed before the age of 5 years, to 3 per 1,000 for those exposed between 15 to 20 years of age, and it was 1·3 per 1,000 for ages over 20 years.

" There is a clear relationship between age at time of exposure and the risk of developing lepromatous leprosy. It is highest for those exposed before the age of five years, decreasing progressively as the age at time of exposure increases. This is true for both males and females."

An interesting finding is that at all ages the risk rate is very much higher for male children, regardless of the age of first exposure. Males at all ages therefore appear to be more susceptible to leprosy than females. *L. Rogers.*

BANCROFT, H., GUINTO, R. S., RODRIGUEZ, J. N. & MARQUES, A. P. **A Note on Familial Relationship and the Risk of developing Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 79–82.

In the Philippines the risk of infection of persons living in a house with a person suffering from lepromatous leprosy has been found to be eight times as great as that of those not known to have had such household exposure ; these conclusions were formed on the basis of 283 families in Cebu island, P.I., with sufficiently complete records for analysis [this *Bulletin,* 1936, v. 33, 931 ; 1942, v. 39, 216 ; 1944, v. 41, 48]. The duration of exposure to infection was expressed in person-years ; that is, each year of life following exposure was counted as a year of risk. Only households in which the primary case was in a member of the family were included. The risk of infection from a neural case was no greater than for the general population. The highest rate of attack—4·31 per 1,000—was in a group exposed to an infected father ; the rates in relation to mother, brother and sister varied between 3·57 and 3·60 only. The infection rates for males were always higher than for females except where the primary case was a mother ; in that case the female rate was 8·10 per 1,000 against 1·95 for males, but that rate was based on too few cases (three females and two males) to be significant. Further inquiries on this important subject are needed. *L. Rogers.*

MOISER, B. **Modes of Transmission of Hansen's Disease (Leprosy).** *Leprosy Review.* 1945, Dec., v. 16, No. 2, 63–6.

The author states that leprosy is undoubtedly a house or family disease, yet in S. Rhodesia 60·9 per cent. of over 2,000 cases failed to give a history of contact with another case. At his hospital cockroaches have been investigated with the help of a trained hospital orderly, who carried out microscopical examinations and found acid-fast " oval-bodies " in 69 per cent. of those obtained in the hospital, or from kraals some distance away. Similar bodies were not found in other insects examined. They were also found in the dried droppings of the insects, in which they survived for 169 days. He says that cockroaches bite man savagely at night, but those caught in native huts, and not fed on leprous material, also were found positive to " Hansen's bacillus ". It is not stated on what ground the acid-fast bacilli in the cockroaches were determined to be those of Hansen, but the author concludes that " these investigations give some reason to doubt an exclusive contagion and infection theory of the transmission of Hansen's disease from man to man."

In an editorial it is recorded that Professor BUXTON was consulted on this paper and he pointed out that cockroaches eat a great variety of types of food, and may be expected to swallow many types of bacteria, some of which may belong to the large group of acid-fast bacilli, which are therefore probably normal inhabitants of these insects. *L. Rogers.*

MONTEL, R., BRUN, Mlle. & MARLIANGEAS, Mlle. La bacillémie lepreuse techniques de laboratoire pour sa recherche. [**Bacillaemia in Leprosy : Laboratory Techniques for its Study.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 261–4, 3 figs.

In this note the author deals with the methods of demonstrating lepra bacilli in the blood. He points out that the organisms are found in the large monocytes, which are more numerous in blood taken from the ear, under pressure, than in that from a finger. They may more readily be demonstrated in blood taken from a vein if 5 cc. are centrifuged after being received in a little citrate solution,

and if a preparation from the leucocyte layer is stained. Numerous bacilli are found in the protoplasm of the large monocytes, and those free in the circulation are derived from ruptured leucocytes. *L. Rogers.*

Mom, A. M. & Basombrio, G. **The Diffusion Factor in Leprous Skin.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 49–59, 4 figs. on 1 pl. [18 refs.]

The diffusion factor dealt with by the authors is measured by injecting into the shaved skin of a rabbit a 1 per cent. solution of trypan blue as an indicator, together with the tissue extract to be tested, and measuring the rate of diffusion around the site of injection. Testicular extract has the highest rate of diffusion. Tests have been carried out to compare the diffusion factor present in normal and in leprous skins, and it has been found that tuberculoid skin has a diffusion action nearly equal to that of normal skin, but that the activity of lepromatous skin is considerably less, and is similar to that of a saline control. The factor in skins containing different numbers of lepra bacilli were also measured, and it was found that the diffusion activity of lepromatous skin is inversely proportionate to the amount of *Myco. leprae* it contains. Further, an extract of lepromatous skin appears to be antagonistic to the diffusion action of an extract of tuberculoid skin. [See also this *Bulletin*, 1944, v. 41, 582.] *L. Rogers.*

Tilden, I. L. **Lepromatous Leprosy : a Reticulo-endothelial Disease. Histopathologic Aspects.** *Amer. J. Clin. Path.* 1945, May, v. 15, No. 5, 165–77, 12 figs. [14 refs.]

This is a detailed and well-illustrated account of the microscopical characters of lepromatous lesions. The author supports the view of Aschoff regarding the reticulo-endothelial system, which is especially involved in lepromatous leprosy, with abundant lepra bacilli in the affected tissues, and negative lepromin tests. The nodules are predominantly composed of histiocytes, mostly spindle-shaped, resembling fibroblasts. The epidermis over a nodule becomes atrophied and the papillary portion is often obliterated. When the tissue is stained with Sudan III there is a striking resemblance to xanthoma, with varying amounts of lipoid material. Countless numbers of lepra bacilli are present, mostly arranged in parallel bundles. The globi are simply large or fused histiocytes, forming giant cells. Another important feature is the absence of any necrosis such as is a typical feature of tuberculous lesions. The liver and spleen commonly show foci of similar involvement of reticulo-endothelial tissues, with circumscribed miliary lepromata most clearly seen in the liver. The lymph nodes are also affected with coarsely vacuolated cytoplasm. The glomerular tufts of the kidneys may show amyloid changes. The lungs are the least affected of the internal organs. Among 16 autopsies, tuberculous complications of leprosy were found in 7. *L. Rogers.*

Davison, A. R. **Notes on a Case of Lymphadenoma complicating Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 38–40.

The main interest in this case is that the development of symptoms of lymphadenoma in a lepromatous case in a European was followed by a remarkable change from repeatedly positive to repeatedly negative bacteriological examinations for lepra bacilli during the last two years of the patient's life. The treatment used at Pretoria was the usual one by subcutaneous and intradermal injection of chaulmoogra esters, under which 20 to 30 per cent. of the neural cases are discharged each year. In the case of lepromatous disease, on the

other hand, 18 years' experience shows that it is almost never cured. The present patient had been segregated at home after spending four years in the institution in a stationary condition except for one reaction. He was re-admitted in December 1941 with lymphadenomatous enlargement of lymphatic glands, liver and spleen, and was given deep X-ray therapy, with only temporary improvement. Earlier examinations showed five positive results for lepra bacilli between November 1937 and April 1940, but eight negative results between the last date and March 1942. He was reported to have died at home in May 1942, and apparently an autopsy was done. *L. Rogers.*

Argüello Pitt, L. & Conejos, M. Lepra tuberculoide (variedad colicuativa). [**Colliquative Type of Tuberculoid Leprosy.**] *Rev. Argentina Dermatosifilologia.* 1945, Sept., v. 29, No. 3, 191–5, 5 figs. [11 refs.]

A man, previously enjoying excellent health, presented himself with a large sore in the right lumbar region, 15×9 cm. Three and a half years before he had fallen from a ladder and bruised this part. The first signs of the present lesion started as a " cyanotic blotch " 4 months before he came to the dispensary, that is, more than 3 years after his fall. The sore was ovoid, with well-defined edge, raised and presenting papules. Parts were hyperaesthetic, other parts were anaesthetic, the skin atrophied, of a reddish cyanotic colour—a cutaneous necrosis with a mild fungoid appearance, gelatinous in parts and bleeding readily when touched. No acid-fast bacilli were seen in the copious sanious discharge nor in sections of portions obtained by biopsy. The lepromin reaction was strongly positive. The appearance was very suggestive of lupus. Photographs show very clearly the lesion, and photomicrographs illustrate the histological changes. In spite of the failure to find Hansen's bacilli, the diagnosis of leprosy in the tuberculoid form, of the lupoid type and of the rare colliquative variety was made. Failure to find the organism was probably due to the colliquative necrosis. *H. Harold Scott.*

Pogge, R. C. **The Frequency of Neuritis in Leprosy. Its Symptomatic Treatment with Intravenous Calcium Gluconate.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 31–7.

At the U.S.A. National Leprosarium, distressing neuritis was found to have occurred in the course of the disease in 56 per cent. of 203 unselected ambulatory patients. It is mainly due to pressure on nerve trunks produced by a lymphocyte infiltration, which may either destroy the function, or result in painful irritation of the nerves, especially the ulna, median, radial, peroneal and superficial cervical, which become enlarged, painful and tender to touch. In 73·7 per cent. of the patients the symptoms persisted for a year or more, so that in the remaining 26·3 per cent. improvement had taken place within 12 months. A greater proportion of improvements should therefore be obtained to indicate good results from any treatment under trial. Routine treatment with either chaulmoogra preparations or with promin did not, within 12 months, have any demonstrable effect on the course of the nerve pains.

Treatment trials showed that mild cases improve on vitamin B, orally, or on heat treatment. In moderate cases about half improve on vitamin B_1 but slightly less under heat ; in severe cases it is necessary to inject vitamin B_1, which is then effective in about half the time. In persistent cases soluble calcium was tried for its sedative influence in decreasing the irritability of nerves, but absorption on oral administration is variable. The author therefore injected 1 gm. of calcium gluconate in 10 cc. of distilled water intravenously (given rather slowly) daily for a week, and subsequently gave one to three

injections a week until the nerve pain became moderate in degree over several weeks. During 1943, 35 patients were so treated without any other medication, with improvement in some 90 per cent. of them. This treatment thus proved palliative in neuritic complications. *L. Rogers.*

SUBRAMANIAM, R. **Deep Reflexes in Neural Leprosy.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 511–12.

The author found that the deep reflexes were present and brisk in cases of neural leprosy with claw-hand or drop-foot ; he thinks that this enables such cases to be distinguished from similar conditions due to peripheral neuritis from other causes, especially when other signs of leprosy are doubtful. The editor comments that the observation has been made before and that there is not general peripheral neuritis in leprosy, which usually affects the superficial nerves that are not concerned with the deep reflexes ; *e.g.*, the peroneal nerve is affected in foot-drop but is not connected with ankle jerk, and the ulnar nerve, whose involvement causes claw hand, is not associated with the biceps and supinator jerks. *J. F. Corson.*

HASSELTINE, H. E. **Pitfalls in the Diagnosis of Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 41–4.

In this note the author points out that a specimen made by the scraped incision method of Wade, in unbroken skin, is the most reliable for the demonstration of lepra bacilli, but that it is rendered still more reliable by repeating the process on the same or another lesion, staining the second slide separately from the first, and relying only on finding the typical bundle arrangement of the bacilli. He quotes cases in support of this view, and emphasizes the difficulties due to the frequent presence of non-leprotic acid-fast bacilli in the skin.

L. Rogers.

HENDERSON, H. J. **Immunological Studies on Leprosy Bacilli.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 45–8.

The author reports another attempt to prepare, from bacteria believed to be the causative agent of leprosy, a product that could be used as an antigen in the precipitin or complement fixation tests with the serum of leprosy patients, or to obtain a product (like tuberculin) of diagnostic value by a skin test. For this purpose he used a preparation of acid-fast bacilli, almost free from tissue cells, from the dried spleen of a leprous patient. A series of nine subcutaneous injections of the acid-fast organism thus obtained, amounting to a total of 180 mgm., were given to each of two rabbits in the course of 23 days. Leprous sera were supplied from the Carville leprosarium for the precipitin test, but it was found that precipitates were formed, not only with human leprosy serum, but also with normal human serum. The method therefore failed to demonstrate the presence of specific leprosy antigen in the human leprous serum.

L. Rogers.

CONVIT, J., AZULAY, R. D., BERMUDEZ, D. & SALGADO, P. **The Lepromin Test in Tuberculous Persons in a Non-Endemic Area.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 60–64, 3 figs. on 1 pl. [10 refs.]

If it is assumed that the response to lepromin is a specific allergic one, then the frequent positive reactions met with in non-endemic regions of leprosy may possibly be explained by assuming that *Myco. leprae* contains a protein similar to that of *Myco. tuberculosis*, and that the reactions are due to prior infection

with the organism of tuberculosis. To test this theory, the response of persons in non-endemic areas in the form of both early and late reactions has been tested. The results, in ten patients with various dermatoses, showed 9 early and 8 late positive reactions. Of four patients with Boeck's sarcoid, three gave negative results and one was weakly positive. At Seaview Hospital, New York, 108 patients with pulmonary tuberculosis were tested; the early (Fernandez) reaction was positive in 43 (70·4 per cent.) of 61 tested and the late (Mitsuda) reaction was positive in 50 (46·2 per cent.) out of 108. *L. Rogers.*

FENNEL, E. A. **Leprosy: Initial Lesion and Surgical Cure. A Case Report.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 83–9.

This paper records the present condition of two surviving leprosy patients in whom the primary lesion was removed surgically many years ago; they were first reported in 1937 [see this *Bulletin*, 1938, v. 35, 300]. The first patient had voluntarily lived and worked in the Hawaii leper settlement. In September 1932 he developed a solitary pink macule on his forehead and a second one a little later; in one of these the typical lepra bacilli were found in 1933, which did not produce any signs of tuberculosis or leprosy on inoculation into guineapigs. Histologically, tuberculoid changes were found in the excised lesions. Repeated subsequent bacterioscopic examinations have all been negative for lepra bacilli and he has remained free from other symptoms of the disease up to the present time, eleven and a half years after the little operation.

The second case is in the female child of leper parents in Hawaii, both of whom had neural symptoms, but she was removed from them at the age of six hours and brought up in a clean nursery [see GOODHUE & MCCOY, this *Bulletin*, 1916, v. 8, 243]. While she was still an infant, a reddish-brown nodule, 12 by 8 mm. in extent and 2 mm. high on the flexor surface of the left forearm had been excised, and a moderate number of lepra bacilli were found in it microscopically. The histology was entirely consistent with a leprous nodule. Seven months after the operation a few atypical acid-fast bacilli were found in a snip from the scar, so she was declared to be leprous and continued to live in the settlement, presumably with her leper parents. At the age of ten, a careful examination failed to reveal any signs of leprosy; at seventeen she married a heavily infected lepromatous leper with marked nodules. In 1937 she applied for and obtained parole and was found, after thorough microscopical examination, still to be free from all signs of the disease. In 1944 she was again examined clinically and showed no evidence of leprosy, so she has remained free from the disease for nearly thirty years. These cases afford a strong argument for early diagnosis.

[It may also be pointed out that these cases strongly support the modern view that leprosy infection usually occurs through the entry of the causative bacilli into the skin through abrasions, etc., including the punctures of insect bites, to form at first an isolated local infection.] *L. Rogers.*

MUIR, E. **Preliminary Report on Diasone in the Treatment of Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 1–6.

In view of the favourable results of the use of the closely allied promin at the U.S.A. Carville settlement, and the favourable results reported from the administration of diasone in tuberculosis, the latter drug has been tried by the author in lepromatous cases in the Trinidad Chacachacare Island leprosarium. Diasone was given intravenously in doses of 0·3 gm., the powder being dissolved or suspended in 1 cc. of sterile normal saline and the fluid filtered through three layers of sterile gauze. The injections were given six days a

week and the dose was gradually raised to 2–8 cc. In view of the anaemia-producing action of the drug, the dosage was controlled by watching the haemoglobin index. The early results—rapid clearing up of lepromatous ulcers and improvement in the general well-being of the patients—inspired their confidence in the treatment, but in some the appearance of anaemia and weakness led to the suspension of the treatment or a diminution of the dosage. Later the injections were restricted to three a week, with dosage varying from 2 cc. to 8 cc. At first twelve cases were treated, but later the number was raised to about 100, in about half of whom the drug was given orally in capsules. If the haemoglobin fell below 78 per cent., ferrous sulphate was given orally.

Beneficial results were noted in the form of general improvement in health, drying up of lepromatous ulcers and flattening of nodules, clearing of nasal lesions and of inflammatory eye lesions and disappearance of chronic fever and lepra reaction. Of 33 cases treated for over three months by intravenous injection, 17 had greatly improved, 15 were slightly improved and 1 remained stationary. Of 10 cases treated orally for over three months, 7 had greatly and 2 slightly improved. In cases treated by either method for less than three months, none showed great improvement, but 36 out of 41 showed slight improvement. There was no evidence that changes in the haemoglobin content influenced the effects of treatment ; liver extract and iron in most cases improved any anaemia. The good effect in clearing up febrile and inflammatory symptoms was noteworthy. The results are therefore encouraging, and are very similar to those produced by promin. *L. Rogers.*

Chorine, V. Action thérapeutique du para-amino-phényl-sulfamide et de l'acétamide employés soit séparément, soit associés dans la lèpre. [**The Therapeutic Action of Sulphanilamide and Acetamide, separately and together, in Leprosy.**] *Bull. Soc. Path. Exot.* 1945, v. 38, Nos. 7/8, 188–95.

In this paper the author records experimental trials of acetamide and " Septoplix " [sulphanilamide], both separately and together, with a control series in rat leprosy. Details of the experiment are recorded, together with a table summarizing the results. Both local and generalized lesions were first produced by inoculating the rats with Stéfansky's bacillus and leaving time for the general development of the infection. The acetamide was given orally in solution in large doses over a period of 117 days. In a second series of animals large doses of " Septoplix " were administered for a similar period. In a third series both were given, but the combination proved to be toxic and the animals wasted. Both drugs caused reduction in the local lesions at the sites of infection and prevented the development of lesions in the internal organs, but no better results were obtained by their simultaneous use than separately. *L. Rogers.*

Lengauer, L. **Palm Oil in Leprosy.** *Leprosy Review.* 1945, Dec., v. 16, No. 2, 67–9.

Working in the Benin province of South Nigeria, the author heard of a leper village which had been founded by an ex-leper. This man was found to have extracted oil from the kernels obtained from available palm trees, and to have used the oil extensively by rubbing it into his skin ; he soon noticed improvement in his health. To increase his food, at low cost, he had also drunk the oil, to the extent of half a teacup at a time. At the end of a year he had recovered, and he then began to treat other leprosy patients in the same way, and soon a village had grown around his solitary hut. At the time of the visit

of the lady doctor the village was very clean, and about 100 lepers looked well. They showed peculiarly smooth skins, and tuberculoid areas and macules seemed to be flattened, as if almost dissolved, although no other treatment had been given. Only lepers from neighbouring villages were admitted. The author decided to try palm oil treatment herself and she found that chronic ulcers did very well under an ointment composed of zinc oxide powder mixed with palm oil. This oil, given orally in place of cod liver oil during the war was also beneficial, and relieved constipation. It is a cheap method of supplementing a deficient diet. *L. Rogers.*

FAGET, G. H. & POGGE, R. C. **Penicillin used unsuccessfully in Treatment of Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 7–10.

This short note records the trial of penicillin in seven lepromatous or nodular cases of leprosy, with negative results as regards the primary disease. Two of them showed recently developed nodules, the third was a specially early case and the other four had more or less advanced lepromatous lesions. Complications included eye, nasal and laryngeal lesions; no beneficial effects were observed in these conditions, with the exception of healing of secondarily infected ulcers in one case. The doses of penicillin used were up to 50,000 to 100,000 units daily for a period of several weeks. In an addendum written six months later, the authors report that during that time no beneficial result attributable to the treatment had been observed in the seven cases first treated. Four others treated with much larger doses had also failed to respond to penicillin. *L. Rogers.*

SLOAN, N. R. **Tracheotomy in Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1944, Dec., v. 12, 11–30, 6 figs.

This paper deals with an extensive experience in advanced lepromatous cases at the Hawaii Molokai settlement, where no less than 13·1 per cent. of "active patients" are wearing tracheal tubes. During a twelve-year period, 146 tracheotomy operations have been performed on 144 patients; information is tabulated on the time from first isolation to operation, and age at time of operation. Leprotic laryngitis is found only in lepromatous cases, and it commences with great thickening of the epiglottis; spread of the disease to the vocal cords produces stenosis requiring operative relief. Increasing hoarseness and dyspnoea, with choking spells, are the main indications for the operation, which should not be delayed too long.

The surgical anatomy and operative procedure are fully described. After the operation a semi-sitting position for a day or two, codeine sulphate in half-grain doses orally before meals for three days, and liquid diet for a day or two are advised. Later the tube should be removed for cleansing twice a day. Relief is quickly afforded. Out of 98 cases tabulated, 14 deaths are classed as post-operative within two weeks, and of the remaining 84, 26 are classed as "tube deaths" in the sense that they were indirectly caused by the laryngeal lesion which necessitated the operation. The deaths from tuberculosis were only 15 to 18 per cent., about half the rate for the settlement at large. Those still living number 46, one of whom has worn a tube for six years.

L. Rogers.

DOW, D. **Occupational Therapy in Leprosy Institutions.** *Leprosy Review.* 1945, Dec., v. 16, No. 2, 57–63.

The author writes from experience at the Dichpali Leprosy Hospital, India, in which there are 800 resident patients, mostly men. He first stresses the

importance of studying the psychology of the patient, as he holds that few, if any, of the patients are "really healthy-minded." The patient's sense of frustration should be removed and he should be helped to resume his place in society, for which purpose he should be provided with suitable occupation and work of a useful nature to restore his self-confidence. Active outdoor agricultural work is best for those fitted for it, but for others cooking and the preparation of grain, etc., house cleaning, the grinding of rice and flour, are suitable occupations; it was not found possible to make weaving profitable. Women are employed in washing and mending clothes, cooking, light gardening, etc. The older children do similar work to that of the women except for cooking. Each patient, on admission, is given a labour classification.

The original 50 acres of the colony have been increased to 450 acres; of these 250 are devoted to agriculture, with the help of irrigation from a tank and wells. The products are of financial importance, but of more importance is the satisfaction and contentment of the patients as the result of doing interesting and productive work. *L. Rogers.*

Leprosy Review. 1945, Dec., v. 16, No. 2, 40–57. **Preventoria. A Symposium on the Care of the Children of Leprous Parents.**

The important subject of the best methods of protection from infection of children born to leper parents is summarized in an introduction by the Editor, Dr. E. Muir. This was sent to several experienced workers for their comments, which are recorded in this important article. The principles discussed are that children are specially susceptible to leprosy and should be separated from infective parents as soon as possible after birth. To effect this, either the infected patient may be isolated, or the child removed to the care of relatives or to a preventorium for such children, usually under the care of missionaries, as in India. It is easier to make such provision in a wealthy country like Brazil, with its 22 preventoria, than in poor countries. In Nigeria the position is difficult, and the rearing of children apart from their parents is injurious to them, for crèches in the tropics are very difficult to run efficiently.

In commenting on the above statement, Dr. Money, of Nigeria, thinks that closed cases are not dangerous even to infants at the breast. He agrees on the danger of rearing infants artificially in the tropics, and, in general, with the principles under discussion. Where practicable the use of wet-nurses is beneficial. Four years' experience of allowing closed cases to retain their children has justified itself.

Dr. Davey, also of Nigeria, is in agreement with the principles. He tabulates information on 3,031 uninfected children of leper parents. The type of leprosy to which 1,985 children actually living with an infected parent were exposed was :—active lepromata in 128, early lepromata in 261, simple neural leprosy in 576, tuberculoid leprosy in 977; in 43 the type was unstated. This constitutes a serious problem, for the cases dealt with form only about one-fifth of those of the province of Owerri, and work on a large scale is necessary to prevent child infections by making suitable provision for the separate accommodation of children of parents with open leprosy. Weaned children should be sent to healthy relations, and should be examined periodically. A small crèche is necessary to accommodate new-born children of lepromatous women in settlements.

Dr. Ross, of Southern Nigeria, in a short note, agrees with Dr. Davey. Dr. Wharton in British Guiana has little difficulty as the sexes are separated at the Mahaica leprosy hospital, and the few infants born are taken over by a relative or guardian, usually within seven days of birth. Dr. Robert Cochrane in Madras recognizes the importance of the problem, but in India, in the case of nearly all the children exposed to serious risk of infection, relatives can usually

be found to take charge of the child, or the lepromatous parent can be isolated. There is still scope for healthy children's homes. Cochrane also advocates the separation of children from night contact with an open case in villages; there is evidence that this procedure produces good results.

Lastly, Dr. John LOWE, of Calcutta, is in agreement with the above opinions, and as a result of his own experience emphasizes the danger of children remaining with leprous parents even for 18 months from birth, for a number of them (25 of which are tabulated) developed signs of the disease later and had to be removed from healthy children's homes. He therefore advises the early adoption of infants by healthy relatives. *L. Rogers.*

HELMINTHIASIS.

SAUTET, J. & MARNEFFE, H. Infestation naturelle de *Planorbis adowensis* Bourguignat, 1879, par *Schistosoma mansoni* au Soudan Français. [**Natural Infestation of *Planorbis adowensis* by *Schistosoma mansoni* in the French Soudan.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 320–21.

In 1942, in the area of Baguineda, near Bamako, French Soudan, where the villagers were heavily infested with rectal schistosomiasis, snails of the species *Planorbis adowensis* were found naturally infested with fork-tailed cercariae. Mice were infested by placing them in water containing the cercariae and adult *S. mansoni* and their eggs were recovered from the mice, especially from the liver. *J. F. Corson.*

HERNÁNDEZ MORALES, F. **The Treatment of Schistosomiasis.** *Puerto Rico J. Pub. Health & Trop. Med.* 1945, Mar., v. 20, No. 3, 322–38. [Refs. in footnotes.] [Spanish version 339–56.]

After a "partial review of the literature" on the treatment of schistosomiasis with emetine and with antimony in its various forms, there follows "an analysis of one hundred and fifty-seven cases of Schistosomiasis mansoni treated with Fuadin." The occurrence of this infection has become more prominent during the last few years in Porto Rico. Many persons are unaware that they harbour the infection, and a large number of apparently healthy youths were rejected for military service on account of it. The disease now constitutes a public health problem of first importance to Porto Rico. Fouadin has been widely used in treatment, with conflicting local views on its efficacy; up to now there has been no proper analysis of the results of its employment. A cure rate of between 50 and 60 per cent. was obtained with Fouadin by the author after one or more courses of treatment of his cases. This is in accord with the experiences of others elsewhere. The criteria of cure were the disappearance of symptoms, of eosinophilia, and of ova from the stools. Ova usually vanished between the fourth and twenty-fifth days (usually by the thirteenth) [whether from the beginning or after the completion of the course of drug treatment is not clear]. Toxic reactions caused by Fouadin were encountered, and in some cases were regarded by the author as severe.

A. R. D. Adams.

LAVIER, G. & STEFANOPOULO, G. L'intradermo-réaction et la réaction de fixation du complément dans la distomatose humaine à *Fasciola hepatica*. [**The Intradermal Reaction and the Complement-Fixation Reaction in Human Fascioliasis caused by** *Fasciola hepatica*.] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 9/10, 302–8. [21 refs.]

The authors review many earlier papers in support of their view that contradictory statements occur in the literature about the value of the complement-fixation reaction for the diagnosis of human fascioliasis. This review is useful because some of the papers summarized in it are not easily accessible or are not often quoted.

For their own work the authors prepared an antigen by Fairley's method, which was also used by STEFANOPOULO and PAYET (*Gaz. méd. de France*, 1938, No. 6, 315) and for the preparation of filarial antigen by STEFANOPOULO and DANIAUD [this *Bulletin*, 1941, v. 38, 156]. *Fasciola* obtained from the slaughter house were dried and powdered. One gramme of this powder was kept in 100 cc. of physiological saline at 37°C. for one day and the supernatant fluid was filtered through a Seitz filter. For use it was diluted 1 : 4 or 1 : 5 or more. This antigen gave immediate intradermal reactions. After 3 to 5 minutes a weal with pseudopodia appeared, which reached 3 cm. in diameter, erythema appearing later. One or two hours later both erythema and weal disappeared, but infiltration of the skin and tissues around the reacting area persisted for 4 to 6 hours; after 24 hours the reaction had disappeared entirely. Delayed reactions were not observed, but some strongly positive subjects showed delayed phenomena such as generalized urticaria, pain and swelling of neighbouring articulations. Two subjects showed nausea, profuse diarrhoea lasting several hours, " lipothymie " and signs of shock. Subjects sensitive to various proteins may give false positives, but their reactions are usually surrounded by a smaller erythematous halo, not more than 1 cm. in width, which disappears very quickly.

For the complement fixation reactions the authors used powdered *Fasciola*, 1 gramme of which was kept in 100 cc. of absolute alcohol at 37°C. for 24 hours, filtered and then evaporated until, when it was evaporated to one-third of its volume, it usually became cloudy. Absolute alcohol was then added to the initial volume and the precipitate disappeared. This final solution formed the antigen. It was usually active at a dilution of 1 : 20.

The sera of five subjects affected with fascioliasis were used. The first had had fascioliasis for ten years; the second had contracted it ten years before but was clinically cured and six months earlier the stools contained no eggs of *Fasciola* and there was no eosinophilia; the third had had fascioliasis for ten years; this subject was described by D'ALLAINES, LAVIER and GANDRILLE [this *Bulletin*, 1943, v. 40, 472]; the fourth had had fascioliasis for 3 years but only a few eggs of *Fasciola* were present in the stools; the fifth had had fascioliasis for 4 months and the positive intradermal reaction obtained was contemporary with the appearance of eggs of *Fasciola* in the stools. The controls were: (1) the sera of 3 subjects infested with *Loa loa*; the infestation of one had lasted 6 years, that of another 7 years, and that of the third 4 years; (2) the serum of one subject harbouring *Taenia saginata*; this subject had been treated for this condition the day before the tests were done; (3) the serum of one subject harbouring *Echinococcus* cysts; (4) two subjects serologically proved to be suffering from syphilis; (5) the sera of 3 subjects without evidence of fascioliasis; no eggs of *Fasciola* were found in the stools of these three subjects after repeated examinations, but one had an eosinophilia of 50 per cent., another a " moderate " eosinophilia, and the third the normal number

of eosinophils. Tests done with a filarial antigen and *Echinococcus* fluid showed that the controls with these infestations were positive to these antigens.

A table gives the results. It shows that the *Fasciola* antigen was specific. All five subjects tested gave positive intradermal and complement fixation reactions to the *Fasciola* antigen and all were negative to the filarial and *Echinococcus* antigens, except the subjects infested with these helminths. None of the controls reacted to the *Fasciola* antigen. The authors remark on the fact that the two syphilitics were negative to it, although it has long been known that syphilitics may give a positive complement fixation reaction to helminth antigens. They quote several papers which record this fact, but point out that FAIRLEY showed that a suitable dilution of the antigen avoids false positives due to syphilis. The authors could not obtain a bilharzial antigen, but suggest that this antigen might give positive results with sera of subjects of fascioliasis because *Fasciola* and *Schistosoma* are nearly related. They suggest that the discordant results obtained by earlier workers may have been due to variations in the method of preparation of the antigen and to the fact that most of the reactions to which the authors refer were done upon sheep, which often lose their infestations but retain antibodies when no flukes can be found in them. One of the human subjects tested by the authors had very strongly positive intradermal and complement fixation reactions, although he had been for some months clinically cured. The implication presumably is that this subject had retained antibodies in his blood during this period. *G. Lapage.*

MARTIN, R., LE ROY, SUREAU, B., BABOUOT, P. & BOURCART, N. Un nouveau cas de distomatose hépatique ; diagnostic précoce par le tubage duodénal. [**A New Case of Hepatic Fascioliasis ; early Diagnosis by Duodenal Intubation.**] *Bull. Soc. Path. Exot.* 1944, v. 37, Nos. 11/12, 359–63, 2 figs. [15 refs.]

The authors say that cases of hepatic fascioliasis have increased in numbers during recent years in France. They mention " epidemics " at Clermont-Ferrers and Lyons. They think that, when a febrile syndrome with marked eosinophilia is encountered, every effort should be made to exclude fascioliasis. Early diagnosis is important because treatment with emetine is especially effective when the flukes are young.

The authors describe the case of a girl, aged 14, who was admitted to hospital with persistent fever lasting a month and a half. The history showed that three months before admission, while the girl was on holiday in the country, she complained of continuous headache, pain in the right hypochondrium, and, at times, bilious vomiting. On her return to Paris the pain and vomiting had ceased, but the girl was thin and had no appetite. Tuberculosis and typhoid infection were eliminated. The liver was painful and enlarged. Painful crises occurred, which resembled hepatic colic. The spleen was palpable and there was slight icterus. Other examinations were negative, except that the blood showed an eosinophilia of 46 per cent. Hodgkin's disease was eliminated by sternal puncture, and the Casoni and Weinberg reactions for hydatid disease were negative. Duodenal intubation then revealed the presence of eggs of *Fasciola*, and examination of the stools subsequently also revealed them. The patient said she had never eaten water-cress (*cresson*), but she was very fond of eating herbs picked casually during her walks.

She was treated with emetine. [The doses given are not stated.] The number of eggs in the stools became smaller and smaller until none was found. The eosinophilia decreased to 20 per cent., but duodenal intubation still revealed eggs of *Fasciola* in the duodenum. A month later two duodenal intubations failed to reveal eggs. The authors remark that the painful enlargement of the

liver which is one of the cardinal symptoms of fascioliasis was absent from this subject; the hepatic symptoms were only transitory. The patient, however, did show a symptom rarely recorded in subjects of fascioliasis, namely, enlargement of the cervical lymphatic glands. The palpable spleen is emphasized by the authors, but this is an exceptional sign. They remark that the coexistence of an irregular temperature with profuse sweats and a high eosinophilia suggests fascioliasis. Duodenal intubation enabled them to diagnose the disease in this subject during the acute hepatic phase, during which young flukes enter the liver before eggs of *Fasciola* appear in the stools. After this stage the subject often gets better and the infestation becomes chronic. In literature supplied to the authors by Professor LAVIER, only 6 out of 127 cases were diagnosed during the acute early phase. Duodenal intubation can establish the diagnosis 15 days before eggs of *Fasciola* appear in the stools, so that emetine, which kills the young flukes more effectively than the older ones, can be given.

G. Lapage.

ZAKHAROV, V. I. [**To the Epidemiology of the Alveolar Echinococcosis in Kazakhstan.**] *Med. Parasit. & Parasitic Dis.* Moscow. 1945, v. 14, No. 4, 33–4. [In Russian.]

SCOTT, J. A. **Hookworm Disease in Texas.** *Texas Reports on Biol. & Med.* 1945, v. 3, No. 4, 558–68, 1 fig. [14 refs.]

"The available data indicate that in most of the parts of Texas where hookworm was once common, the infection now occurs only in a very small percentage of the population and clinical cases are a rarity. In a small area in the extreme eastern part of the state the infection is more common, but even there it is not more than half as frequent as it once was. A rough estimate based on the meager information available indicates that probably not more than 10,000 persons are infected and the number of clinical cases probably does not exceed 1,000. The improvement over conditions known to exist 30 years ago has probably been due in part to the control programs of various sorts. On the other hand, in spite of depression set backs, there has been a general lifting of the economic level of living in these areas which has undoubtedly been reflected in the decrease of hookworm prevalence through improved nutritional and sanitary conditions. There is a great need for further investigations to determine the exact public health status of hookworm disease at the present time and to define the conditions which might be modified so as to effect further control."

FISCHER, F. K. Beitrag zur Kenntnis der Anguilluliasis oder Strongyloidosis. [**Contribution to our Knowledge of Anguilluliasis or Strongyloidiasis.**] *Schweiz. med. Woch.* 1946, Feb. 16, v. 76, No. 7, 137–40, 1 fig. & 1 chart. [21 refs.]

The author states that the records of strongyloidiasis, particularly reports on it in the German Ruhr district, show that it often co-exists with hookworm infestation. He briefly outlines the life-history of *Strongyloides stercoralis* and reminds us that auto-infection can maintain an infestation, the skin-penetrating larvae being able to develop either in the large intestine or in faecal matter adhering to the anal region, and to penetrate either the mucosa of the large bowel or the perianal skin. The author states that few clinical papers report strongyloidiasis as a serious disease, although ASKANAZY (*Cent. f. Bakt.*, 1 Abt. Orig., 1900, v. 27, 569) found in sections of the upper part of the duodenum and in the ileum severe damage done by the larvae, which burrow into the mucosa of these parts of the intestine. The severity of any helminth infestation is, however, affected by the numbers of helminths present.

The author reports in great detail his study of one patient infested with *S. stercoralis*. This patient was an Australian infantryman, born in 1919, who had served in Palestine and Greece and had been captured in Crete in 1941. An epidemic of diarrhoea broke out in the unhygienic prisoners' camp in Crete and the patient was severely ill in hospital. Transferred to Salonika and later to Athens, he suffered repeated attacks of severe diarrhoea and abdominal pain with flatulence. Treatment [unspecified] was given for "dysentery" in Athens. Here he suffered from haemorrhages from the penis. After escaping and living in Athens for a time, he was recaptured and sent, in 1942, to Italy, where he was fairly well until, in June 1942, he had another attack of diarrhoea, abdominal pain and flatulence lasting five weeks. He was again fairly well until June 1943, when the same symptoms recurred. In that year he reached Switzerland, where, in October 1943, he developed cough, sore throat and a rash resembling sudamina. Suspected of having measles, he was sent to hospital, where he had an attack of diarrhoea with blood and mucus in the stools and abdominal cramp. Examination revealed little likely to account for his illnesses. On October 20, 1943, a differential leucocyte count showed that there were "5⅓" per cent. of eosinophils in his blood. Agglutination tests ruled out typhoid, paratyphoid, bacillary dysentery and brucellosis. The bloody diarrhoea continued, but the rash disappeared. On October 25 there were "16⅔" per cent. of eosinophils in his blood. Neither *Entamoeba histolytica* nor its cysts were found in the stools, but these did contain larvae of *S. stercoralis*, and eggs of *Ascaris* and *Trichuris*. On November 1, the subject was much the same and "Chenosan" expelled 5 *Ascaris*. There were then "32⅓" per cent. of eosinophils in the blood. On November 6 there were 40,000 white blood cells, of which "72⅔" per cent. were eosinophils. Bone marrow obtained by sternal puncture revealed a very greatly increased formation of eosinophils. [Details of the differential counts of blood and bone marrow cells are given.] On subsequent dates the eosinophilia was as follows: Nov. 8, "77⅔" per cent. (*i.e.* 3,000 of 40,000 white blood cells); filariform larvae of *Strongyloides stercoralis* were then numerous in the contents of the stomach and in bile obtained by duodenal sound; the bile also contained eggs of *S. stercoralis*; Nov. 9, 78 per cent.; Nov. 12, 81½ per cent. (*i.e.* 18,900 of 23,400 white blood cells). From this date this very high eosinophilia gradually decreased and with its decrease the patient felt much better and the diarrhoea ceased. On December 24, however, the subject had marked pain in the penis and perineum with small haemorrhages from the urethra and swelling of the corpora cavernosa extending back to the perineum; there were very painful erections and reddening of the skin on the under side of the penis. The white blood cells rose from 9,800 to 16,000 with "41⅓" per cent. of eosinophils. This condition disappeared in three days. By January 12, 1944, no larvae of *S. stercoralis* were found in the duodenal contents. The patient left for Australia with an eosinophilia of "35 to 45 per cent." A subsequent message from Australia said that he had felt well until February 1945, but still had larvae of *S. stercoralis* in his stools.

Discussing this case, the author points out that *Strongyloides* can be distinguished from hookworm by the fact that its eggs are never found in the stools; they can only be obtained either by a very drastic purge or by duodenal intubation, and then are seen to be always embryonated, while the eggs of hookworms are not. The author never found the rhabditiform free living adult generation. Repeated skin penetration by the filariform larvae of *S. stercoralis* may cause sensitivity of the skin, so that itching and the formation of weals may occur in the perianal region. A condition resembling "creeping eruption" may be established, and FÜLLEBORN (*Klin. Woch.*, 1925, v. 35, 1709) described the formation of similar weals on the skin of subjects infested

with *S. stercoralis* after injection into the skin of an antigen made from dried and powdered *Strongyloides* larvae. The urethral haemorrhages and the pain and itching of the penis of this patient are ascribed by the author to this cause. When the patient washed these parts with soap, and applied 10 per cent. *Ung. Hydrarg. praec. alb.*, these symptoms did not reappear [*cf.* the infestation of the genito-urinary tract with *S. stercoralis* described by WHITEHILL and MILLER, this *Bulletin*, 1945, v. 42, 576].

Enormous eosinophilia, such as that here recorded, is unusual. It has been ascribed to an allergic condition in subjects with an "eosinophil constitution," but Fischer suggests that in this patient a "toxic" effect was responsible. The patient was treated for 9 months, but both adult *Strongyloides* and its larvae remained. He was, however, in good health, when he had an eosinophilia of 30 per cent. and larvae were not so numerous in his stools after treatment.

Gentian violet in doses of "6×0·04 g." daily for about 3 months produced no improvement; larvae remained in the stools. Gentian violet was therefore combined with the following additional treatment, which was given at the same time. The patient was prepared with a saline purge. In the forenoon he had an enema of 1 per thousand thymol solution or benzine water and on the following morning oil of chenopodium (two doses of 18 drops with 1 hour's interval between) followed at intervals of one hour by three doses of one teaspoonful of *sulphur depuratum*. In the resulting diarrhoea, massive numbers of dead *Strongyloides* larvae were found. This treatment was given 3 times at intervals of 8 days at the same time as the gentian violet and it produced no untoward results. No better results were obtained with filix mas, santonin or thymol. Carbon tetrachloride, tetrachlorethylene, atebrin, intravenous neosalvarsan, intravenous arsacetin, kamala, areca seed and Fouadin were all ineffective. Phenothiazine was also ineffective and had to be given up on the seventh day because it caused the excretion of "porphyrin". A final attempt to cure the subject by duodenal intubation of 1 per cent. aqueous solution of gentian violet caused nausea, vomiting and collapse and the subject's departure to Australia prevented further trials of it. The author says that he gave in this way 250 cc. of the 1 per cent. solution of gentian violet at the rate of 50–60 drops a minute. [CRAIG and FAUST, *Clinical Parasitology*, 3rd edition, 1943, 253, recommend 25 cc. See also v. ENGEL, this *Bulletin*, 1945, v. 42, 49, who also began with 250 cc. but, because of its severe effects, substituted 100 cc. at a slower rate and claimed to have cured his subject. See also the other references mentioned in this abstract and PALMER, this *Bulletin*, 1945, v. 42, 135.] *G. Lapage.*

DROUET, P. L., THOMAS, C., HERBEUVAL, R. & FAIVRE, G. Hémorragies du vitré et ascaridiose. Nouvelles hémorragies du vitré et néphrite consécutive à une intradermo-réaction à la toxine ascaridienne. [**Haemorrhages of the Vitreous and Ascariasis. Fresh Haemorrhages of the Vitreous, and Nephritis, following an Intradermal Reaction to the Ascarid Toxin.**] *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1945, Nos. 24/25, 342–4.

The authors describe the occurrence of bilateral haemorrhages into the vitreous humour of the eye of a woman aged 60. Clinical examination revealed nothing likely to account for these, but the blood contained 22 per cent. of eosinophil leucocytes and, about a year later, when the haemorrhages recurred, 18 per cent. of eosinophils. The stools contained eggs of *Ascaris* and *Trichuris*. Santonin at first failed to expel any nematodes (perhaps because the doses were too small), but later it expelled some ascarids. The eosinophilia persisted. The authors discuss possible causes of the haemorrhages, but come to

the conclusion that they were associated with the ascariasis. Haemorrhages in the course of ascariasis have been noted by CASSOUTE and VAGUE (*Soc. Péd.*, 1934, Jan. 16). MATHIEU and FAIVRE (*Soc. Méd. de Nancy*, 1945), reported repeated haematuria coinciding with the expulsion of an *Ascaris* through the mouth, but haemorrhages of the vitreous have been still more rarely reported in subjects infested with various parasites. In this subject, however, the eosinophilia persisted. The complement deviation reaction failed to reveal the presence of antibody in the blood, but this was not surprising, because this antibody appears, the authors state, only when the cuticle of the nematode is ruptured or its permeability is altered by its death (*cf.* hydatid cysts). The authors did intradermal reactions on this subject with the dilute coelomic fluid of ascaris derived from the subject under consideration. With a dilution of 1 : 100 of this fluid they obtained on two separate occasions a non-pruriginous papule the size of a 50 centime piece which appeared in a few minutes and disappeared after 1 hour. The same test gave the same result two days later. Two days later still a test was done with " Ascaris toxin " [the precise method of preparation of this is not stated]. Almost immediately this " toxin " produced a non-pruriginous cockade reaction 2½ cm. in diameter, with a haemorrhagic centre and erythematous periphery sprinkled with petechiae and an intermediate zone. A control intradermal reaction on a subject also infested with *Ascaris* but without any signs of similar haemorrhages into the vitreous produced in half an hour a non-pruriginous, erythematous weal which disappeared in three-quarters of an hour. In several subjects not infested with *Ascaris* neither early nor delayed reactions were obtained.

About 4 hours after the intradermal reaction the subject under discussion showed a renewed haemorrhage in the temporal region of the right eye ; she complained of lumbar pain. Next morning there was palpebral and malleolar oedema. The urine contained albumin, granular and hyaline casts, renal cells, red blood cells and polymorphonuclears. There were no other clinical symptoms. Two days later the oedema had disappeared ; the urine contained a few erythrocytes and less albumin and urea but no casts. There was a blood eosinophilia of 10 per cent. Some days later the subject went home without any trace of nephritis.

The authors thus obtained experimental proof that " *Ascaris* toxin " was the cause of the haemorrhages into the vitreous of this subject, but the nephritis and haematuria were new factors. The authors ascribe it, not to an anaphylactic reaction, but to what TZANCK has called renal intolerance ; it resembles allergic nephritis. The intradermal reaction done with " *Ascaris* toxin " precipitated in this previously sensitized subject a true phenomenon, namely, a local haemorrhagic crisis which became general and attacked the eye and the kidney, in which there was a temporary allergic haemorrhagic nephritis. We know that certain organs, and especially the kidney, are apt to show haemorrhagic reactions. Perhaps there was some individual cause in this subject to explain the localization of the haemorrhages in the eye.

Among authors who have studied the intradermal reaction to *Ascaris* " toxin " are CICULESCU (*Soc. Méd. des Hôpitaux de Bucarest*, 1927, April), AVRAMOÏU and DANCILLA (*Rev. Péd. si Puéricult.*, 1937, December), and SIMONIN (*Thèse*, Nancy, 1919). *G. Lapage.*

THOMPSON, K. J., RIFKIN, H. & ZARROW, M. **Early Filariasis in Young Soldiers. Clinical and Pathologic Analysis.** *J. Amer. Med. Ass.* 1945, Dec. 15, v. 129, No. 16, 1074–9. [13 refs.]

A series of 200 young American soldiers infected with filariasis [presumably Bancroftian] has been studied during a period of two years. As a result of

prolonged clinical observation, with biopsies of superficial lymphatics or lymph glands, and the employment of a skin test, using for this a *Dirofilaria immitis* antigen in various dilutions, a concept of the pathology of early filariasis has been elaborated. The early stages of the disease are very different from the later classical elephantoid stage described in textbooks. After describing the six clinical groups into which their cases fall, the authors conclude that there is no one symptom or sign that is constantly found in all cases of the early disease, other than persistently enlarged and palpable lymph nodes. These, in the earliest acute phase, are large and soft, but later they shrink and become hard. The differential diagnosis of the gland enlargement of early filariasis is dependent on biopsy of lymph cords and lymph glands and on the employment of the skin test described in detail by the authors. The biopsies were performed on superficial lymphatics and glands, and, where funiculitis was present, material was taken from the pampiniform plexus under local anaesthesia. In the examination of lymph glands the authors found that the axillary glands were more likely to give a distinctive microscopic finding than the inguinal glands, and they warn against the obvious temptation to take the latter purely on account of easier accessibility. They regard the lymphatic involvement during the first phase of the early stage of the disease as systemic rather than focal in origin, and prefer to examine a lymphatic cord or gland bizarrely situated, as long as it shows evidence of acute involvement. There is little to be learned from the incidence of primary lymph gland involvement.

As a result of their studies they conclude that early filariasis can be divided into three phases :—(*a*) the early acute, or allergic ; (*b*) the subacute ; (*c*) the early chronic, as follows :—

(*a*) The *early acute phase* is characterized clinically by sudden lymphangitis with an accompanying lymphadenitis of the regional lymph glands lasting for 3–4 days. Fever and constitutional upset are minimal. Though the lymphangitis extends as a rule in the normal direction, in some cases it is retrograde or centrifugal in its extension. The attacks may recur over 8–9 months, or they may be single events. At the height of the lymphangitis in the arm, leg or structures of the cord there may be lymphadenitis and lymphangitis bizarrely situated elsewhere. Funiculitis and epididymitis were seen in about half the cases ; usually these are unilateral, although succeeding attacks may involve the opposite side ; they may subside rapidly with the declension of the lymphangitis. In association with them the inguinal glands are slightly enlarged, and there is commonly an associated small hydrocele and a brawny oedematous thickening of the scrotum. The cord may become as thick as the thumb and the vas deferens as thick as a lead pencil.

During this stage no microfilariae are to be found in the blood, even when a concentration technique (Knott's) is used ; eosinophilia is slight or moderate. Biopsy shows hyperplasia of the lymph follicles, with eosinophilic infiltration and general oedema of the lymph glands. In many cases filarial worms are actually to be seen in the gland ; but the pathological picture, apparently, is not dependent on the visible presence of the worms. Lymph glands remote from the site of the lesion and containing no worms or microfilariae show similar pathological changes—thus supporting the view that the changes are of a generalized systemic nature and not purely focal.

Biopsy of an acute filarial lymph channel shows thickening, oedema and eosinophilic infiltration of the wall. The lumen is filled with an acute thrombus in which the eosinophils are pyknotic and aggregated into a necrotic amorphous mass. Filarial worms or microfilariae may or may not be seen in the lymphatic vessel.

(*b*) In the *subacute phase* there is no lymphangitis, swelling or oedema, but a feeling of heaviness and aching of the involved part is experienced, with little

clinical evidence of abnormality. There may be mild recurrent oedema, fleeting in nature, after heavy physical effort. Some small shotty lymph glands may be felt, which do not resemble the soft enlarged glands of the previous phase. Histologically there is a proliferative granulomatous reaction in the lumen and the walls of the lymphatics, and in the lymph glands. There is macrophage proliferation, with the formation of small epithelioid-cell foci throughout the lymph cords and walls of the lymphatics, and of the periglandular connective tissue. There may be degenerating filarial parasites surrounded by concentric laminae of collagenous tissue in the centre of epithelioid tuberculoid foci.

When the worms have degenerated and become unrecognizable, the central zone consists of pink-staining caseo-necrotic material with radially arranged macrophages—these lesions resemble true tubercles and have been named tuberculoid focal granulomata. There is an epithelioid-cell endo-lymphangitis and peri-lymphangitis, as described by HARTZ. The periphery of the tuberculoid focal granulomata may contain accumulations of spindle-shaped fibroblasts, indicating the onset of the next stage.

(*c*) The *last stage* of early filariasis. In 10 cases observed at this time there were no circulating microfilariae in the blood, and the infective type of lymphangitis of the advanced chronic elephantoid stage had not yet developed. Cases in this stage of early filariasis may subside completely and not progress further. This stage occurs at a variable time after the onset of the first stage (*a*), and is characterized by chronic swelling, with or without a pitting oedema, associated with aching of the extremity. It has no distinctive micro-pathology and lacks many of the clinical features of the classical elephantoid state. There is a generalized reticulo-endothelial hyperplasia with irregular fibrosis. The lymphatic vessels may be reduced to a fibrous cord—the condition which has been called, by ZUCKERMAN, obliterative endo-lymphangitis—and developing fibrosis is the predominant feature of the pathology.

The blood pictures of all the cases were normal in most respects; 25 per cent. had a white cell count of over 10,000 per cmm.; 34 per cent. had an eosinophilia which averaged between 10 and 15 per cent., and never rose above 28 per cent. Data are given relative to four illustrative cases.

[This paper should be consulted in the original by those interested.]

A. R. D. Adams.

PRATT, Caroline K. **The Use of Adrenalin in Acute Tropical Lymphangitis or Elephantiasis.** *Bol. Asoc. Med. de Puerto Rico.* 1945, Oct., v. 37, No. 10, 412–13.

As it has been suggested that the attacks of lymphangitis in filariasis are associated with allergy, adrenaline therapy was tried in eight cases of the disease in Porto Rico. Adrenaline [presumably 1 in 1,000 solution] was injected hypodermically, an initial dose of 0·5 cc., then 5 minims every 4 to 6 hours. After the first injection the sensation of heat in the limb became less and this relief lasted for one to three hours. The bone pain, nausea, and headache became less or disappeared after the third or fourth injection, and within 24 hours the redness of the skin had gone.

No microfilariae were found in the blood either before or after the administration of adrenaline. The total number of blood leucocytes did not exceed 11,000 per cmm. and no material change in the differential count was observed. In one case a relapse occurred 24 hours after the end of the injections.

J. F. Corson.

OLIVER-GONZÁLEZ, J. & MORALES, F. H. **Common Antigens among Filarial and other Nematode Parasites of Man.** *J. Infect. Dis.* 1945, Sept.–Oct., v. 77, No. 2, 92–5. [13 refs.]

The authors prepared antigens from the adults of *Dirofilaria immitis* of the dog and *Litomosoides carinii* of the rat, and from microfilarial larvae of *Wuchereria bancrofti*. With these antigens they did intradermal tests on subjects harbouring microfilariae of *W. bancrofti* and on others without these, some of whom harboured *Ascaris*, *Necator* and *Trichuris*. The serological diagnosis of infestations with *W. bancrofti* by means of antigens derived from other species of nematodes has been attempted by TALIAFERRO and HOFFMAN [this *Bulletin*, 1931, v. 28, 214] who used extracts of *Dirofilaria immitis*, by FAIRLEY [*ibid.*, 679] who also used *D. immitis*, by ACTON and RAO [*ibid.*, 1933, v. 30, 699] who used *Dracunculus medinensis*, by MOHR and LIPPELT [*ibid.*, 1941, v. 38, 518] who used *Contortospiculum rheae* of the South American ostrich, and by CULBERTSON, ROSE and DEMAREST [*ibid.*, 1944, v. 41, p. 771], who used *Litomosoides carinii* of the rat. The present authors say that the cross reactions obtained by these workers may be explained as being due to a common antigen or group of antigens found in both filariids and other nematodes. Similar common antigens are found among the Trematodes. Thus "many of" the mammalian schistosomes may be used for the preparation of antigens for the diagnosis of human schistosomiasis; they may even be obtained from trematodes less closely related to human schistosomes, such as *Fasciola hepatica* and *Pneumoneces medioplexus* [see CULBERTSON and ROSE, this *Bulletin*, 1943, v. 40, p. 471].

The microfilariae of *W. bancrofti* were obtained by the method of OLIVER-GONZÁLEZ and BERCOVITZ [this *Bulletin*, 1945, v. 42, p. 219]. A one per cent. suspension of the nematode material (adults or microfilariae) in 0·85 per cent. physiological saline was incubated at 37°C. for one hour and then left overnight at room temperature. The supernatant fluid was diluted 1 : 100 and used as stock for making other dilutions. In the same way antigens were prepared from *Ascaris lumbricoides* and *Necator americanus*. The antigens were sterilized by repeated incubation for 30 minutes in a water bath at 56°C. and tested for sterility on thioglycollate medium. The tests were done by injection of 0·1 cc. of the antigen dilution, and of control antigens, intradermally into the volar surface of the forearm. Reactions were read after 10 minutes. The bleb following the injection and the weals were outlined on the skin with ink and traced upon transparent film placed over the skin. A reaction was considered positive when an increase in size of the bleb could be observed immediately after the injection. The antigen obtained from *L. carinii* seemed to be the most potent; it gave the largest number of positives. The antigen obtained from *W. bancrofti* seemed to be the least potent; it gave negative reactions in dilutions of 1 : 5,000.

Two groups of subjects were tested. Group A consisted of 180 Porto Ricans aged 12–40 years. Of these, 90 had microfilariae of *W. bancrofti* in the circulating blood at night, and 90 had none. None of these 180 had shown symptoms of filariasis. Group B consisted of 36 American soldiers and sailors recently transferred to Porto Rico from the United States. None had microfilariae in his blood and none had shown symptoms of filariasis. Tables give the full results obtained at the various antigen dilutions used (1 : 200 to 1 : 100,000). The authors concluded that the number of positive reactions obtained with the three filariid and the other antigens used, in subjects with microfilariae in their blood, was not significantly different from the number of positives obtained with the same antigens in subjects without microfilariae in their blood. Thus, in group A, 94 per cent. (41 out of 45) subjects with microfilariae and 87 per

cent. (38 out of 40) subjects without microfilariae were positive to a dilution of 1 : 10,000 of the *D. immitis* antigen. The percentage of positives and negatives to the other dilutions of the various antigens was of the same order.

With regard to cross reactions with other nematodes, the authors found that, among the 180 subjects in group A, 127 (70 per cent.) had either *Ascaris*, *Trichuris* or " hookworm ", *i.e.* 68 (75 per cent.) of the 90 with microfilariae in their blood and 59 (66 per cent.) of the 90 without microfilariae. None of group B, however, had intestinal nematodes. All the subjects in group B were negative to dilutions of 1 : 200 and 1 : 10,000 of the three filarial antigens, except two subjects (12 per cent.), who gave positive reactions to *Ascaris* antigen and also to physiological saline. The authors think it unlikely that these two positive subjects were suffering from early or low-grade infestations. They point out that Culbertson, Rose and Demarest (*loc. cit.*) and Bozicevich and Hutter [this *Bulletin*, 1944, v. 41, 1055] also obtained negative reactions to 1 : 200 and 1 : 8,000 dilutions of rat and dog filariid antigens in Americans not infested with nematodes.

These results suggest that skin reactions to filariid antigens may be greatly influenced by the presence of other nematodes. The presence of group-specific substances is also suggested by the fact that 85 per cent. (17 out of 24) of subjects in group A without microfilariae in their blood gave positive reactions to 1 : 10,000 dilutions of *Ascaris* antigen, and 75 per cent. (15 out of 20) of subjects with microfilariae gave positive reactions to 1 : 10,000 dilutions of hookworm antigen. Similar results were obtained in those members of group A who had no microfilariae in their blood. The authors think that subjects with any of the nematodes may become skin sensitive to antigens from any member of the group. They refer to Bachman and Rodriguez Molina [this *Bulletin*, 1933, v. 30, 222], who reported positive skin reactions to hookworm antigen by subjects without hookworm infestation, but with infestations with *Ascaris* and *Trichuris* ; to Rodhain and Dubois [*ibid.*, 1932, v. 29, 83] and Brunner (*J. Immunology*, 1938, v. 15, 83) who found that *Ascaris* antigens give positive reactions when other species of nematodes are present ; and to Mazzotti and Osorio [this *Bulletin*, 1944, v. 41, 957] who obtained 13 per cent. of positive reactions to *Onchocerca caecutiens* antigen by subjects not infested with this species.

The percentage of positive reactions obtained by the authors to the 1 : 10,000 dilution of *Dirofilaria immitis* antigen in the Porto Ricans of Group A, namely 87 per cent., far exceeds the estimated percentage infestation of the general population of Porto Rico, namely 9·7 per cent., recorded by Hoffman, Marin and Burke [this *Bulletin*, 1932, v. 29, 768].

The skin test for filariasis can thus only be used with safety when other species of nematodes are absent. This is a serious limitation of the test, because members of the Forces and others will be exposed to both filariids and intestinal species. *G. Lapage.*

Mazzotti, L. & Osorio, Maria T. **The Diagnosis of Enterobiasis. Comparative Study of the Graham and Hall Techniques in the Diagnosis of Enterobiasis.** *J. Lab. & Clin. Med.* 1945, Dec., v. 30, No. 12, 1046–8.

" Examinations for the diagnosis of enterobiasis were carried out in 430 individuals using both the Hall and Graham techniques. The percentage of positive results obtained was 32 per cent. with the Graham method and 16 per cent. with the technique of Hall."

DEFICIENCY DISEASES.

CHURCHILL, M. H. **Dietary Deficiency Diseases among Prisoners of War.** *J. Roy. Army Med. Corps.* 1945, Dec., v. 85, No. 6, 294–8.

This paper is based on notes of nearly 500 cases of deficiency disease occurring in prisoners of war in Singapore and Thailand during the period 1942–1945. Elaborate examination was often not possible, and treatment was difficult owing to lack of supplies.

A type of amblyopia was a common condition : the first cases appeared within 4 months of the prisoners going on to the Japanese ration scale. In rather less than half the sufferers there was an association with some better recognized symptom of deficiency. The outstanding symptom was blurring of vision, but this was preceded by smarting of the eyes, lachrymation and photophobia. The failure of sight was often progressive and severe ; in other cases it progressed to a certain stage and then remained stationary ; in others, again, it varied, improving when there was any substantial improvement in the diet. Two factors seemed to be concerned in producing the condition : dietary deficiency and intense sunlight. There was no apparent correlation between the defect in vision and the ophthalmoscopic appearances. About half those examined showed some degree of cupping or excavation of the disk.

Observations on pellagrous conditions, on beriberi, and on some other aspects of vitamin deficiency are recorded. No evidence was found of deficiency of vitamins A and C. *H. E. Harding.*

KRISHNAN, B. G., RAMACHANDRAN, S. & SADHU, K. **The Treatment and Prevention of Vitamin-B_1 Deficiency in Infants : a Public Health Experiment.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 521–4.

Infantile beriberi is far from uncommon in the Northern Circars of Madras Presidency and an inquiry centre was set up in Cocanada in 1942. This paper gives an account of its activities. The authors start by describing the disease, which is " vitamin B_1 (or thiamin) deficiency in infants " of beriberi mothers, and which differs in most respects from beriberi in adults. The symptoms may set in abruptly in an infant apparently in good health, with cyanosis, dyspnoea and tachycardia, and may run a fulminating course ending fatally in a few hours. In others, there is colic with fits of screaming, vomiting, diarrhoea and convulsions. Still more chronic cases occur, which are characterized by pallor, vomiting and signs of marasmus. Aphonia is a common symptom. Injection of vitamin B_1 brings about dramatic cures, even in infants seemingly moribund.

At the Cocanada centre 1,145 infants had been treated by the end of 1945 ; all were breast-fed and their ages ranged up to 12 months, but most of the cases were in those under 6 months and the peak was at about 4 months. Of the total, 980 (85·5 per cent.) were discharged as cured, but in 68 (6·9 per cent.) of these relapse or recurrence took place at intervals up to 3 months. Only 16 deaths occurred. Prophylaxis—giving one tablet of the vitamin (1 mgm.) to the mother once each day during 3 months before and 6 months after delivery —was tried, and of 54 so treated, who had previously lost babies, 28 had infants which developed the disease in spite of the vitamin administration. Twelve others with a similar history, but who were not given prophylactic vitamin tablets, had 8 living children, all of whom developed infantile beriberi and were cured. The dosage used, 1 mgm. tablets, administered regularly seemed to be of some value, but was probably inadequate, for the women were living on a diet very deficient in vitamin B_1.

The centre is becoming very popular; a considerable number of mothers travel more than 100 miles to bring their children for treatment.

The subject is of sufficient importance to be included in public health policy; the measures suggested are an all-round improvement in diet and, in the meantime, to make the treatment more widely known and applicable by establishing more of these centres. *H. Harold Scott.*

CHARTERS, A. D. **Beriberi in a European.** *East African Med. J.* 1945, Dec., v. 22, No. 12, 397–401.

SPRUE.

BLACK, D. A. K. & FOURMAN, P. **The Stools in Clinical Sprue.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 492–4.

This investigation was made to determine the incidence in sprue patients of the "characteristic" stool—pale, bulky, frothy, offensive and of high fat content—and to see whether some simpler method of examination of the stool could replace the chemical estimation of fat, which needs laboratory facilities.

A consecutive series of 150 stools of sprue patients were examined with the naked eye and microscopically, and a chemical estimation of the total and split fat was made. The patients had been kept on a "sprue IV" diet containing 70 gm. of fat during the preceding three days.

The results are given in four tables which show the relation of total fat content to pallor of the stool, and the relation of fatty acid content to the finding of fatty acid crystals by microscopic examination. "Two-thirds of the stools examined had over 25 per cent. of fat; pallor of the stool and the presence of fatty acid crystals were commoner in stools of high fat content, but 34 out of 102 stools with increased fat showed neither pallor nor fatty acid crystals. Chemical analysis is therefore needed to determine with certainty whether a stool contains an excess of fat." *J. F. Corson.*

SPIES, T. D., LOPEZ, G. G., MENENDEZ, J. A., MINNICH, Virginia & KOCH, Mary B. **The Effect of Folic Acid on Sprue.** *Southern Med. J.* 1946, Jan., v. 39, No. 1, 30–32.

In view of the remarkable haematological and clinical response of macrocytic anaemia to the oral or parenteral administration of synthetic folic acid [see SPIES *et al.*, this *Bulletin*, 1946, v. 43, 375] the authors were interested to find out the effect of folic acid in the treatment of sprue. In selecting the cases of sprue the following criteria were applied: (1) The patient must have a macrocytic anaemia with a red cell count of 2,500,000 or less, and a colour index of over 1; (2) the patient must not have been treated recently enough to interfere with the evaluation of the effect of folic acid; (3) there must be no complicating disease which might be lethal during the course of the study; (4) the bone marrow must contain megaloblasts and have the typical erythroblastic arrest seen in macrocytic anaemia; (5) the patient must have steatorrhoea and loss of weight.

After satisfactory base-line clinical and laboratory determinations had been made on three selected patients, each was given daily 200 mgm. of folic acid by mouth; the drug was administered in divided doses each of 100 mgm. stirred in water.

On the third or fourth day of treatment each patient voluntarily stated that he was gaining weight and had regained his appetite. The reticulocytes

increased on the fourth or fifth day and reached a peak on the sixth or seventh day. Associated with this rise in reticulocytes there was a subsequent rise in the red blood cell counts and in the haemoglobin content of the blood. The stools tended to become normal in form, and occasionally they appeared almost normal for one to two days, but it must be stressed that under the conditions of the study, namely restriction to a high carbohydrate diet devoid of meat, the stools did not become and remain entirely normal; similarly liver extract does not completely cause the stools of patients with sprue to become normal. Associated with the haematopoietic response there was a striking gain in strength, vigour, and appetite.

Although pernicious anaemia is included in the group of macrocytic anaemias, its natural pathogenesis is somewhat different from the mechanisms involved in the macrocytic anaemia of sprue, pregnancy, pellagra, and nutritional macrocytic anaemia. It may be that folic acid in food occurs as a conjugate, and, in view of CASTLE'S work, that in pernicious anaemia the enzymes are unable efficiently to liberate the folic acid, whereas in sprue, pellagra, pregnancy and nutritional macrocytic anaemia the folic acid, or substances that act similarly, are made more available. An explanation must also be found for the fact that a fairly large amount of folic acid is required to produce a maximum haematopoietic response, in contrast to highly potent liver extract in which the active substance is apparently smaller. However, it has been shown that synthetic folic acid has a striking anti-anaemic effect in five types of macrocytic anaemia, namely Addisonian pernicious anaemia, nutritional macrocytic anaemia, and the macrocytic anaemia of sprue, pellagra and pregnancy. *F. Murgatroyd.*

HAEMATOLOGY.

HYNES, M., ISHAQ, M. & MORRIS, T. L. **Anaemia in Indian Army Recruits.** *Indian J. Med. Res.* 1945, Oct., v. 33, No. 2, 271–84, 3 graphs. [11 refs.]

The haemoglobin levels, red cell counts and packed cell volumes of some 600 Indian army recruits, mostly drawn from the labouring classes, were determined by carefully standardized methods, using venous blood.

The most striking feature was the superiority of the nursing sepoys over other recruits of the same race. Only 8 per cent. of the nursing sepoys were anaemic (Hb less than 13 gm. per 100 cc. blood), and 80 per cent. had levels over 14 gm. Hb, a fact possibly explicable by the higher social status of these recruits. About 25 per cent. of the Punjabi ambulance sepoy and ward servant recruits were anaemic, and 5 per cent. had less than 11 gm. Hb; while about 40 per cent. of United Provinces ward servants and Madrasi sweepers were anaemic.

The haemoglobin levels were significantly lower in Mohammedans than in Hindus, and as the Mohammedan has fewer dietary prejudices than the Hindu, these differences were probably due to economic causes. There was no correlation between age and anaemia.

Hookworm infestation was present in about 60 per cent. of both Madrasi and United Provinces recruits, in about 30 per cent. of the Punjabi ambulance sepoys and nursing sepoys, but in only about 12 per cent. of the Punjabi ward servants. There was a marked correlation between hookworm infestation and anaemia, the degree of anaemia increasing with the weight of infestation; men with even very light infestations had haemoglobin levels significantly lower than those of the non-infested men. The connexion between anaemia

and hookworms was, however, not constant ; one-third of the recruits with under 11 gm. Hb had no infestation, while one-third of those with moderately heavy infestations had over 14 gm. Hb. It was concluded, therefore, that hookworm infestation was a secondary factor in the production of the anaemia.

Over three-quarters of the total anaemia in all classes was normocytic (MCV between 80 and 100 cμ.). In both Madrasis and Punjabis about 60 per cent. of the normocytic anaemia was normochromic (MCHC 30 per cent. or over), but in United Provinces recruits 90 per cent. was normochromic and only 10 per cent. hypochromic (MCHC less than 30 per cent.).

In both Madrasis and Punjabis about 20 per cent. of the total anaemia was microcytic (MCV less than 80 cμ.), and about half the microcytic anaemias were normochromic. In United Provinces recruits only 2 of 39 cases of anaemia were microcytic, and both these were normochromic.

Only five very mild cases of macrocytic anaemia (MCV of 100 cμ. or over) were found. Two were from Madras, two from United Provinces and one was from Sind. One of the Madrasis had a hypochromic macrocytic anaemia, and the remaining four were normochromic ; none had bilirubinaemia or splenomegaly. No case of macrocytic anaemia was found in the Punjabis.

In both Madrasis and Punjabis about 45 per cent. of the anaemia was hypochromic, but in United Provinces recruits the proportion was only 10 per cent. The frequency of hypochromic anaemia was greater among the severe anaemias ; where the haemoglobin value was below 10 gm., 11 out of 13 cases were hypochromic. Extreme hypochromia (MCHC less than 28 per cent.) was rarely seen except in the more severe anaemias, only three of fifteen such cases having over 11 gm. Hb. Contrary to expectation, hypochromia, a sign of iron-deficiency, was not more frequent in men infested with hookworms than in the non-infested.

Whereas 56 per cent. of recruits with haemoglobin levels over 14 gm. had a MCHC of 32 per cent. or over, this value was exceeded in only 35 per cent. of the normochromic anaemias. This difference is statistically highly significant, but while red cells with a MCHC below 30 per cent. are certainly unsaturated, those with a MCHC a little over 30 per cent. may be saturated or unsaturated.

The change to army life and diet, in itself, considerably improved the anaemias of the recruits, but a group given in addition 6 grains of ferrous sulphate daily improved very much more. On recruitment, both the group given iron and the untreated group contained about 45 per cent. of anaemic men, and about 25 per cent. of men with haemoglobin levels of 14 gm. or over. After 3 months' training, 31 per cent. of those not receiving iron were still anaemic and 50 per cent. had 14 or more gm. Hb., whereas of those taking iron, only 8 per cent. were anaemic and 80 per cent. had levels of 14 gm. or more. Two months later, those taking iron had improved still further, but no significant change had occurred in the others. The observations showed that, in both groups, men with initial haemoglobin levels of between 14 and 14·9 gm. were capable of improvement. All types of anaemia seemed to respond equally well. Hookworm infestation had no measurable influence on the haemoglobin regeneration in either group, even when the infestation was moderately heavy. The responses of the Madrasis and Punjabis were very similar, but in both groups the haemoglobin classes of United Provinces recruits were slightly inferior. The red cell count and packed cell volume both rose with the haemoglobin, and were significantly higher from one month onwards in those taking iron than in those not taking it.

There were many puzzling features about this universal response to iron therapy. Only 4 per cent. of the men who benefited from iron had typical iron-deficiency anaemias, and only 30 per cent. had any of the usual signs of iron deficiency. Furthermore, nutrition workers have deduced from analyses

that even the poorest Indian diets have an iron content adequate even for the greater needs of women. It is possible that a great part of the iron of the poor Indian diet is for some reason not assimilable. Apart from the original chemical form of the iron, there is little knowledge of the influence on its absorption of mineral balance and such interfering substances as phytic acid. It is also possible that some dietary deficiency that may be the major cause of the anaemia, prevents the utilization of iron, and that when that factor is replaced, iron is still necessary to build new haemoglobin. Finally, it is possible that the benefit observed was due not to iron, but to traces of some other metal present in the ferrous sulphate and deficient in the common Indian diet. Beyond speculation, however, it is clear that most recruits benefited from a daily dose of ferrous sulphate. The authors suggest that only when the haemoglobin level exceeds 15 gm. should it be considered satisfactory; a standard reached by only 25 per cent. of the newly joined recruits other than nursing sepoys. *F. Murgatroyd.*

Moore, C. V., Bierbaum, Olga S., Welch, A. D. & Wright, L. D. **The Activity of Synthetic *Lactobacillus casei* Factor ("Folic Acid") as an Antipernicious Anemia Substance. I. Observations on Four Patients: Two with Addisonian Pernicious Anemia, One with Nontropical Sprue and One with Pernicious Anemia of Pregnancy.** *J. Lab. & Clin. Med.* 1945, Dec., v. 30, No. 12, 1056–69, 4 figs. [30 refs.]

"Clinical and hematologic remissions were induced in two patients with Addisonian pernicious anemia by the daily oral administration for ten days of 30 mg. and of 100 mg. of synthetic *L. casei* factor ("folic acid"), respectively. One patient with macrocytic anemia of nontropical sprue and one patient with pernicious anemia of pregnancy responded in a similar manner when given daily 20 mg. of the preparation intravenously.

"Reasons are given for interpreting these results as indicating that *L. casei* factor possesses antipernicious anemia factor activity. It is pointed out, however, that the material must be proved effective parenterally in much smaller doses, and over a much longer period of time, before it can be accepted as being closely similar in action to (or identical with) the effective principle present in liver extracts."

Discombe, G. **Criteria of Eosinophilia.** *Lancet.* 1946, Feb. 9, 195–6. [12 refs.]

As it became necessary accurately to determine the eosinophil counts of a series of patients, and as the limited staff was insufficient to undertake by ordinary methods the large number of differential counts required, the possibility of using a simpler and more rapid technique for the determination of eosinophilia was considered.

Although cover-slip films are less subject to errors due to differential distribution of cells than are smears on slides, mathematical calculations showed that increases in the proportion or absolute number of cells present to the extent of 1–5 per cent. in blood can be detected with certainty by a differential count only if very large numbers of cells are counted in cover-slip preparations. However, methods for counting eosinophils in a haemocytometer have been devised, and as the uncertainty of such counts varies with the square root of the number of cells counted, the error can readily be made as small as desired by counting more cells. The following method was therefore adopted:—

Blood is diluted with the fluid (1 per cent. aqueous eosin Y and acetone, 5 volumes each; distilled water to 100 volumes; this keeps for some weeks), and after mixing, is allowed to stand for 5 minutes. After the pipette has been

shaken vigorously by hand for 2–3 minutes, a Fuchs-Rosenthal chamber is filled; and when the cells have settled (1–2 minutes), the preparation is examined with a 2/3 in. objective and a ×10 eyepiece under the most brilliant illumination tolerable. In such preparations the unstained leucocytes cannot be seen, and the eosinophils stand out as deep red particles, easily countable; clumping is unusual, but if it develops the preparation must be rejected. Careful investigations showed the method to be entirely satisfactory. For routine work, two pipettes should be filled, and one Fuchs-Rosenthal chamber filled from each. If the whole ruled area (3·2 sq. mm.) is counted and 104 or more eosinophils are found, corresponding to a count of 325 per cmm., it is certain that eosinophilia is present. The normal range of eosinophils is up to 240 per cmm., and not more than 1 per cent. of normal subjects should have counts above this.

It was possible to demonstrate a mild degree of eosinophilia (400–500 per cmm.) in most quiescent asthmatics, but the method was principally used in following the treatment of patients with injections of gold salts, as it has been shown that toxic manifestations of chrysotherapy are associated with eosinophilia, and as routine differential counts have been recommended for the early detection of this toxicity. *F. Murgatroyd.*

SIMONIN, P. & GIRARD, J. Syndrome de Loeffler à forme micronodulaire chez une asthmatique. [**Loeffler's Syndrome in an Asthmatic.**] *Semaine des Hôpitaux de Paris.* 1946, Feb. 21, v. 22, No. 7, 288–90, 4 figs.

VENOMS AND ANTIVENENES.

AHUJA, M. L. & BROOKS, A. G. **A Suggested First-Aid Treatment for Cobra Bite with Carbolic Soap Solution.** *Indian Med. Gaz.* 1945, Sept., v. 80, No. 9, 461–3.

As long ago as 1924 the observation was made that soaps could detoxify snake venoms, and CARMICHAEL [this *Bulletin*, 1928, v. 25, 291] and CESARI & BOQUET [*ibid.*, 1938, v. 35, 435] showed that sodium ricinoleate was antitoxic *in vitro* to *Crotalus* and *Vipera aspis* venoms.

The authors have tested the action of many substances—colloidal metals, dyes, biological products—to ascertain their detoxifying powers against cobra venom in pigeons, but all were ineffectual. They then tried various soaps and obtained success with emulsions of Lifebuoy carbolic soap, which is to be found in most homes. The soap in 5 per cent. emulsion, infiltrated in doses of 1–2·5 cc. at the site of inoculation of the venom into pigeons of about 300 gm. weight, was effectual against 0·4 mgm. of venom when injected even as late as 1½ hours afterwards. Fourteen survived out of 18, whereas all of 10 untreated died. Even in those which did not survive, death was delayed for several hours. This delay would in many cases enable antivenene to be obtained and, in the authors' experiments, where the soap was followed by antivenene, even as long as two hours later, many survived larger doses still of the venom.

The authors give details of the method which they recommend. If a finger is bitten, a tourniquet is applied at the base of the finger and another above the elbow; if a toe, at the base of the toe and above the knee; then the 5 per cent. soap emulsion (which could be kept ready at the local dispensary, with a sterile syringe) should be injected, 0·5–1·0 cc. at points surrounding the bite—5 cc. in all could be given—and bleeding encouraged by crucial incisions with a razor-blade. Potassium permanganate they regard as valueless and even harmful,

as it may cause sloughing and gangrene. The soap must not be given intravenously and never as a substitute for antivenene ; it is purely a *first-aid treatment.*

The authors ask that it may be tried more widely and invite reports, especially regarding the following points, for information :—

" (*a*) Was the snake definitely identified as a cobra ?
(*b*) Site and details of bite.
(*c*) Interval elapsing between bite and injection of soap solution.
(*d*) Quantity of soap solution injected.
(*e*) Antivenene (including period after bite at which serum was given ; dosage and whether administration was intravenous).
(*f*) Other details with regard to local reaction, symptoms and progress of the case." *H. Harold Scott.*

DERMATOLOGY AND FUNGUS DISEASES.

EPSTEIN, E. **The Lichen Planus—Eczematoid Dermatitis Complex of the Southwest Pacific. A Study of 65 Cases.** *Bull. U.S. Army Med. Dept.* 1945, Dec., v. 4, No. 6, 687–94.

In an introductory paragraph to this paper, Epstein records that, when it was written, the dermatoses contracted overseas were assuming a major aspect in the disabilities suffered by the armed forces, and that those serving in a medical unit which received evacuees from all battle fronts developed a healthy respect for the skin-injuring factors in the Southwest Pacific, particularly in New Guinea and the adjacent islands. The malady, which he names " the lichen planus—eczematoid dermatitis complex " (known to the troops as " jungle rot "), was the most frequent cause of evacuation for skin diseases from this area. Of a series of 65 cases exhibiting the malady, 34 per cent. were in the 25 to 29 age group, and 35 per cent. were older than 35 years of age ; the sex incidence was approximately equal, race did not seem to be important, brunettes were more commonly affected than blondes. Usually the patients had spent three to six months in New Guinea before developing an eruption. The first lesion frequently appeared on an exposed area. Occasionally a generalized oedematous desquamative dermatitis developed in a few days, but in most cases from one to three months were required for full efflorescence. The lesions were of three types, two of which co-existed in more than half the patients. The first type was an aberrant variety of hypertrophic lichen planus, the lesions being purplish, coalescent nodules, having smooth, scaly, warty or pseudo-desquamative surfaces. The face, palms and soles were frequently affected. The eruption, which might be either localized or generalized, did not tend to follow the usual distribution pattern of lichen planus. Sometimes marked atrophy or pseudoatrophy followed the disappearance of the primary lesions. The details in which, despite its general appearance, the eruption differed from true lichen planus were : atypical localization, occasional atrophic sequelae, abnormal histological features, absence of typical lichen planus papules, marked pigmentation and frequent transformation into an eczematoid, exfoliative, dermatitis-like eruption. In the second form, the eruption was eczematoid and affected especially the legs, hands, forearms, neck and ears ; the lesions, erythemato-violaceous in colour, were flat and covered with branny scales. The underlying skin was often thickened. In the more acute varieties, the lesions oozed. The nails showed changes such as those which occur in eczematoid eruptions of the extremities. Sometimes generalized exfoliative dermatitis supervened. The third variety

was a generalized, exudative, oedematous, desquamative eruption, similar to many post-arsenical dermatoses. The skin was thickened, bluish-red in colour, and desquamated freely ; these abnormalities were accompanied by intractable and severe pruritus. Loss of hair from the scalp and body were frequently noted. In some instances the temperature was slightly raised. Oedema of the feet, ankles, and sometimes of the face occurred. Occasionally, general lymphadenopathy was noted. Changes in the nails (including hypertrophy, or atrophy and splitting) were common. As the dermatitis subsided, lichenoid papules frequently appeared ; lost hair was usually replaced.

In diagnosis, the finding of lichenoid nodules in a patient with exfoliative dermatitis was the most important feature. As all the patients had been exposed to a hazard of malaria, this complication was considered in all febrile cases.

As the lesions of the three varieties of the eruption faded, hyper-pigmentation was a noticeable feature. In some cases it suggested the aftermath of lichen planus ; in others it was more diffuse. The colour varied from brown to a deep shade of blue-black, shades of brown being the most common. Freckles and moles tended to become darker. Depigmentation was also noted ; in a negro who suffered from the lichen planus type, many areas of hyperpigmentation with interspersed areas of vitiligo persisted after the rash had faded.

It was impossible to determine the frequency of each of these types of dermatitis, as most patients manifested two or more types at some time during their illness. When the predominant clinical features were tabulated at the time of observation it was found that of 65 cases, 53·8 per cent. presented the localized lesions of the second type of eruption described above ; 26·1 per cent. presented an eczematoid, generalized exfoliative dermatitis-like eruption, and 20 per cent. manifested the hypertrophic lichen planus form of the malady.

The laboratory findings were as follows :—Patients with oedema were suffering from hypoproteinaemia, the albumin-globulin ratio being about 1 : 1 (normal 2 : 1). The total serum proteins were usually between 4 and 5 mgm. per cent. The blood calcium was usually low, 8 to 8·5 mgm. per cent. being the average in severe exfoliative cases. The blood phosphorus level was raised, ranging from 4·5 to 5·5 mgm. per cent. Eosinophilia was not a feature of the disease, and neither anaemia nor leucocytosis was usual, but one patient developed a fatal aplastic anaemia one month after the onset of a localized exfoliative dermatitis. Epstein states that analyses of urine, serological investigations and stool examinations were " not contributory " (? of relevant information).

Microscopical investigation of all forms of the eruption gave interesting results. The more common eczematoid type of lesion showed comparatively regular findings, consisting of parakeratosis, exfoliation of the corium, mixture of leucocytes and red blood cells with the keratin, normal or absent stratum granulosum, oedema of the rete with prominence of the prickle cells, acanthosis, normal basal-cell layer or one undergoing hydropic degeneration, marked regular elongation of the papillae to simulate psoriasis, dilatation of the vessels, and oedema of the upper portion of the derma. A dense cellular infiltrate was present, varying from polymorphonuclear leucocytes in the acute phase to lymphocytes in the chronic phase and with some eosinophils, fibroblasts, and histiocytes. " While this infiltrate was basically superficial, it had a tendency to surround the hair follicles, sebaceous glands, and sweat glands and to dip into the deeper portions of the corium. The skin appendages were normal."

" In the lichen planus forms, the picture varied. In some, typical lichen planus was present with thickening of the stratum granulosum, the plate-like acanthosis, and the superficial band-like infiltrate. In others, the architecture resembled that described as characteristic of the eczematoid lesions ; in many, features of both types were present in the same section. In some, atrophic

changes were prominent. In two, follicular plugging, hyperkeratosis, widely patent follicles, hydropic degeneration of the basal-cell layer, atrophy of the epidermis, superficial perivascular, perifollicular and periglandular infiltration suggested lupus erythematosus. The pigmentary changes were found to be produced by clumps of pigment in the upper portions of the derma. Both intracellular and extracellular masses were seen."

The patients usually improved as soon as they left the Southwest Pacific, but the disappearance of the eruption might take many months, for temporary exacerbations or recurrences usually occurred. The prognosis seemed better in the lichenoid examples than in those with desquamative changes. The pigmentary sequelae cleared slowly. In this series of 65 cases, death occurred in one patient from aplastic anaemia and toxic hepatitis. The frequent mild relapses suggested that the patients might become " dermatological cripples ", their skin being abnormally sensitive to many possible irritants because of the damage caused by the disease.

Treatment was not specific and was not very efficacious. Oily applications usually gave most relief ; a cream formed by mixing equal parts of Lassar's paste (without acid) and ung. aq. rosae was satisfactory. The eruption was not influenced by sulphonamides or penicillin. The effects of intravenous injection of 10 per cent. glucose with insulin and thiamin chloride were studied ; apparently it was of less benefit in this condition than when administered in cases of exfoliative dermatitis due to arsenic. The results of superficial X-ray therapy were indeterminate. In view of the hypoproteinaemia and oedema, the patients with the more severe eruptions received a high protein diet ; intravenous infusions of plasma were also indicated in such cases. Hypocalcaemia suggested that a high calcium diet with vitamin D should be given.

Epstein discusses the aetiology of these eruptions at some length, but agrees that the cause is unknown. In his series, patch tests with atabrine [mepacrine] gave negative results. Wet dressings containing this drug did not aggravate the eruption, and several patients took atabrine for attacks of malaria without aggravation of the dermatitis. He states that most of the available evidence points to the importance of environment ; he regards cutaneous mycotic infections as unlikely to be precipitants of the condition, and dismisses both allergy and infectious processes as causal factors. Whilst he emphasizes that there is little clinical evidence to support this theory, he suggests that consideration should be given to the possibility of lack of vitamins B and A playing a part in the aetiology.

[This paper was written in 1944, and publication has been delayed for reasons of security. At that time the author evidently regarded this malady as being numerically of consequence. Possibly he has since revised his views.

The British experience has been that, although the malady is serious to the individual, relatively few cases have occurred. Nevertheless, Epstein's contribution merits careful perusal by those engaged in studying this problem. It is interesting to find that he notes that pruritus is usually much less marked in the lichen planus type of the malady than in the type associated with eczematoid lesions.

An earlier abstract concerning this subject will be found in this *Bulletin*, 1946, v. 43, 149]. *R. M. B. MacKenna.*

NISBET, T. W. **A New Cutaneous Syndrome occurring in New Guinea and Adjacent Islands. Preliminary Report.** *Arch. Dermat. & Syph.* 1945, Oct., v. 52, No. 4, 221–5.

This is yet another article dealing with the lichenoid eruption called by E. EPSTEIN (1945, see above) the " lichen planus-eczematoid dermatitis complex of the Southwest Pacific."

Nisbet's report is founded on his military experiences in a base section which included practically all the tropical part of Northern Australia, where a large number of United States troops were concentrated at the time ; shortly after the beginning of the Buna campaign in the early part of 1943 his unit received a large number of casualties, the majority suffering from cutaneous diseases. Many presented a bizarre eruption which accounted for more than 80 per cent. of the total number of patients with skin diseases received from New Guinea. He describes the various agents which were considered possible factors in the cause of the eruption ; these included avitaminosis, malnutrition, contact dermatitis from an unknown jungle plant, and sensitization to bacteria and fungi. Later he was posted to another base in New Guinea, and was able to determine that the eruptions in reality constituted a single clinical condition, which had never been noted previously in that locality either among European residents or natives.

Nisbet classifies and describes the eruptions as being of three principal types : (*a*) patchy eczematoid ; (*b*) hypertrophic lichenoid ; (*c*) generalized exfoliative. He states *inter alia* that involvement of the external ears is frequently pathognomonic in the first variety, that pyrexia (of 101–102°F.) is common among patients exhibiting the second type, who may have lesions on the eyelids, conjunctival injection, keratitis and, occasionally, corneal ulceration ; and that the eruption of the generalized exfoliative type is usually a sequel to the patchy eczematous or to the hypertrophic lichenoid varieties.

Many of the patients suffered from relatively mild eruptions which remained more or less stationary during long periods, or which completely disappeared when properly treated. However, a slow progression or recurrence of the malady was the rule. Complete recovery seldom occurred so long as the patient remained in New Guinea, but Nisbet saw 150 patients improve considerably during a voyage of 21 days' duration to the United States, although the living conditions on board were mediocre and the weather was extremely warm. At an Australian Army hospital on the Australian mainland, he was informed that the average period of hospitalization among men of the Commonwealth Army, after they had been evacuated to Australia because of this malady, was approximately three months, complete recovery usually occurring in this time.

He warmly advocates penicillin for the treatment of the severe generalized exfoliative and eczematoid forms of the disease, 150,000 units being given in the first 24 hours, and 80,000 units daily thereafter. [The total dosage is not stated.]

In a footnote Nisbet states that his report was first submitted in November 1944, at a time when it was considered inadvisable to mention quinacrine [mepacrine] hydrochloride as the aetiological agent. He believes that the additional information which has since been obtained confirms his original belief that quinacrine can be inculpated as the factor responsible for this unique dermatitis [contrast the views of EPSTEIN, above]. *R. M. B. MacKenna.*

SCHMITT, C. L., ALPINS, O. & CHAMBERS, G. **Clinical Investigation of a New Cutaneous Entity.** *Arch. Dermat. & Syph.* 1945, Oct., v. 52, No. 4, 226–38, 9 figs.

This is another paper concerning the lichen planus-eczematoid dermatitis complex, and it records the observations made on 47 patients from the South-west Pacific area. It differs slightly in detail from previous reports, but in substance confirms the work of several other writers.

The authors state that the syndrome invariably commenced with an initial eruption composed of a wide variety of cutaneous lesions none of which had

definite diagnostic features. This prodromal rash might consist of : (1) round or irregular superficial scaly patches, resembling a fungus infection ; (2) discrete and confluent pink or red pinhead-sized vesicles and papules, like miliaria ; (3) variously sized round or elongated skin-coloured or slightly elevated lesions of various sizes, which were " welt-like " but neither pruritic nor evanescent ; (4) simple erythematous patches which soon became scaly and progressed to an exfoliating dermatitis ; (5) variants of the preceding. The hands, including the palms, the axillae, the soles and the groins were the sites most commonly affected. These initial eruptions were followed in 2–8 weeks by the appearance of characteristic firm violaceous elevated papules and nodules 0·8–4·0 cm. in size. At first the lesions were soft and smooth ; later they became leathery and verrucose. The authors note that the large elevated papules and nodules never arose from the coalescence of small papules. The patients suffering from the malady only in mild degree presented only widely separated groups or patches of violaceous papules with an occasional verrucose nodule. In addition, many nodules and plateau-like elevated patches with the same violaceous colour also occurred. Occasionally the initial eruption was entirely replaced by the characteristic nodules ; in other instances the original eruption persisted and even progressed. For example, the superficial scaly fungus-like patches in some cases increased by peripheral extension and formed an extensive background for the nodules. The weal-like early manifestation sometimes progressed to form characteristic purplish nodules which comprised the entire secondary picture, the surrounding skin being entirely normal. In some cases there was an accompanying localized erythroderma which gave the surrounding skin a deep red magenta colour. In other patients, with more severe eruptions, an acute exfoliative dermatitis occurred ; this began at a period between the primary eruption and the development of the characteristic nodules, or simultaneously with the development of the nodules. In two cases the elevated lesions underwent necrosis, and punched-out ulcers formed.

Sessile warty excrescences, which usually occurred on the suprapubic regions and on the inner surfaces of the thighs, were noted in the more serious cases.

The covered parts of the body were involved more frequently than the exposed areas, but the upper eyelids were almost constantly affected, although the remainder of the face was rarely involved. Approximately one-third of the patients presented discrete and confluent, tense, grayish white papules on the lower lip, and reticulated, streaked, firm, greyish white patches on the buccal mucosa and the lateral and dorsal surfaces of the tongue. Occasionally the area adjacent to the urinary meatus and the mucosa of the anus were involved.

Subjective symptoms were not associated with the beginning of the eruption, but as the primary lesions progressed, moderate to severe pruritus was common. The itching continued until after the characteristic elevated secondary lesions were well established, after which time it gradually diminished. Constitutional symptoms were present only in those persons who exhibited widespread erythroderma or generalized exfoliative dermatitis.

The sequelae noted were pigmentation, cutaneous atrophy, alopecia, thickening, pitting or total loss of the nails, and reduction or absence of sweat and sebum secretion on areas which had been severely affected. The authors noted that pigmentation of the posterior surfaces of the neck and shoulders was frequently seen, although the eruption had not affected these areas.

Many laboratory investigations were carried out ; the only observation of significance was the presence of malarial parasites in about one-third of the patients.

Biopsy of infiltrated papules or nodules showed that the microscopical appearances were remarkably constant. The degree of hyperkeratosis varied somewhat, but the acanthosis and the thickening of the stratum granulosum were similar in all sections. Rete pegs were found to be elongated; the papillae were widened and their capillaries dilated, whilst chromatophores containing brown, coarsely granular pigment were present in their apices. Similar chromatophores were also present in the epidermis. A diffuse inflammatory reaction was always present, and was confined to the superficial portion of the corium except in the regions of sweat glands or capillaries, when it extended to the deeper layers of the dermis. The inflammatory reaction was composed of lymphocytes and plasma cells, eosinophils and a few neutrophils.

The authors are convinced that the eruption is caused by mepacrine; they reached this conclusion after making various observations, including the re-administration of the drug to nine patients who showed complete or almost complete clearance of their eruption. In four of these patients, whose eruptions had been severe, new characteristic violaceous papules developed in three to fourteen days; two patients had a return of exfoliative dermatitis; three persons who had had only moderately severe eruptions developed mildly erythematous patches, but did not develop characteristic papules during a period of two weeks in which the drug was administered.

Case-histories of seven patients are given. In assessing their observations, the authors state that the interval between starting to take the drug and the appearance of the eruption was never less than one month; the longest interval was eleven months and the average interval was three and one-half months. There was no relationship between this interval and the severity of the eruption, but the length of the period during which use of the drug was continued after the eruption appeared probably influenced the severity of the malady. The application of irritating ointments, containing sulphur or salicylic acid, often caused rapid and widespread evolution of papules and nodules, and seemed to act as a precipitating factor. The dosage of mepacrine influenced the occurrence of the eruption; some persons tolerated the drug in routine prophylactic amounts, but when the prophylactic dose was increased, or when larger amounts were taken to combat malarial symptoms, the eruption appeared within two weeks. This was considered to indicate that a saturation level existed, and that the rash was due to toxicity of the drug, rather than to idiosyncrasy or intolerance.

[In this report is included a brief but adequate discussion of the differential diagnosis of the malady. There are no new suggestions with regard to therapy. The reader will note the reference to co-existing malarial infection in one-third of the patients. Since the publication of this article G. M. FINDLAY (below) has contributed an analysis of the records of the West African Command concerning the problem of lichenoid eruptions and mepacrine. The European personnel of this Command represents a highly mepacrinized population for, in March 1943, mepacrine was introduced to suppress malaria; the usual period on mepacrine for this purpose has been 18 months, but many persons have taken it for 2–3 years. Nevertheless, there has not been any significant increase in the incidence of lichen planus or in maladies resembling lichen planus since 1943. From the experience in this Command, Findlay concludes that it would not be easy to claim any relationship between the incidence of lichen planus and the administration of mepacrine. He implies that in his Command it would be difficult to claim a similar relationship between lichen-planus-like eruptions and the drug in question. Opinions, therefore, seem to be sharply divided concerning the aetiology of these eruptions, and probably it is wisest in the present state of our knowledge to regard the symptom complex under review as

being a malady in which two possible aetiological factors are mepacrine and climatic conditions.] *R. M. B. MacKenna.*

i. LANCET. 1945, Dec. 1, 711–13, 2 figs. [14 refs.] **Atypical Lichen Planus and Mepacrine.**

ii. FINDLAY, G. M. **Mepacrine and Lichen Planus.** [Correspondence.] *Lancet.* 1946, Feb. 16, 252.

i. A skin disease resembling lichen planus occurred during the recent war in the Allied Armies serving in malarious countries. Both sexes were affected and it was thought that mepacrine caused it or was one of the causes. Its occurrence was kept secret lest false or exaggerated rumours should alarm the troops, but now that the war is over many papers on it will probably be published; hitherto most of the published work has been American.

The incidence in the South-West Pacific area was estimated to be about two to three cases per thousand persons who took mepacrine regularly for some months; another estimate was one case per thousand, and in British troops even lower than this.

The eruptions resembled atypical forms of lichen planus; they included a non-weeping type, a lichenoid eruption with eczematous lesions, a generalized dermatitis like exfoliative dermatitis and followed by lesions of lichen planus, and a pustular eruption replaced while healing by lesions like hypertrophic lichen planus. The rash was usually generalized, the face being involved as a rule, the scalp sometimes, and sometimes the buccal mucosa, while the extremities including the palms and soles were usually more affected than other parts. Itching was usually less than in true lichen planus. [See also the paper by EPSTEIN, above.]

Several references to American papers are given, particularly one issued by the Surgeon-General's office in Washington, and the question whether mepacrine was a cause is discussed, the conclusion being that this question will remain controversial until more facts are published.

ii. FINDLAY refers to the above leading article and records in the following table the incidence of lichen planus in European and African troops in West Africa.

Year	European troops		African troops	
	Number of cases	Incidence per 1000 strength	Number of cases	Incidence per 1000 strength
1941 ...	2	0·34	1	0·02
1942 ...	3	0·22	4	0·05
1943 ...	1	0·07	2	0·01
1944 ...	4*	0·37	5	0·05
1945 ...	2*	0·15	5	0·09

* Includes 1 naval case.

African troops were never on suppressive mepacrine and European troops only began to take it in March 1943, and have continued to do so ever since, many having taken it for two or three years. The author concludes that the incidence of lichen planus was not aetiologically related to the administration of mepacrine. [See also a paper by RAINE, *Bulletin of War Medicine*, 1946, v. 6, 366, on skin diseases among the troops serving in the Solomon Islands.]

J. F. Corson.

CURTIS, A. C. & OWENS, B. B. **Beta Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in the Treatment of Urticaria.** *Arch. Dermat. & Syph.* 1945, Oct., v. 52, No. 4, 239–42.

Considerable evidence has been presented by Sir Thomas LEWIS [*The Blood Vessels of the Human Skin and their Responses*, London, 1937] to support the conclusion that a diffusible substance is responsible for the development of urticarial lesions. This material, H substance, is liberated by injured cells, and is said closely to resemble histamine in its action. Apparently it causes local vaso-dilatation and weal formation by direct action on the capillary wall, whilst the flare noted in " the triple response " is possibly due to chemical stimulation of sensory nerve endings in the skin, which brings about widespread vasodilatation through the mechanism of the axon-reflex. Nevertheless, the evidence that histamine is the substance responsible for urticarial lesions is indirect, for it has never been isolated from a weal, and not all investigators agree that it plays any part in the development of this lesion.

Recently, beta dimethylaminoethyl benzhydryl ether hydrochloride has been synthesized ; it belongs to a new and distinct group of pharmacological compounds which may be termed antispasmodics.

Messrs. Parke Davis and Company have apparently given the name of Benadryl to this compound, and Curtis and Owens report the effect of the drug when administered to 18 patients suffering from various types of urticaria.

Benadryl is a stable, white, crystalline, water-soluble compound of low toxicity. It appears to be well tolerated by adults in doses of 50–100 mgm. given orally, 1–5 times daily. In the series of cases described, 11 responded with complete disappearance of the urticaria, except for an occasional non-pruritic lesion which would appear for a short time. Three patients improved, although their lesions did not entirely disappear—a large number of the weals were not pruritic. Four patients did not respond to the doses given. In only one case were there toxic symptoms of weakness and giddiness, severe enough to necessitate the discontinuation of the drug ; the symptoms disappeared promptly when the use of Benadryl was discontinued. Two patients complained of drowsiness and muscular aching, but one of these continued to take Benadryl for seven months without other ill-effect.

Benadryl is palliative only. Chronic urticaria, pruritus, angioneurotic oedema and dermographia recur promptly when the use of the drug is discontinued.

[If the claims made for Benadryl are substantiated by further investigation, it would appear to be a useful and relatively safe compound for the relief of many cases of chronic urticaria in which careful clinical investigation has failed to find a cause.] *R. M. B. MacKenna.*

BURNS, E. L., MOSS, Emma S. & BRUECK, J. W. **Mycetoma Pedis in the United States and Canada.** *Amer. J. Clin. Path.* 1945, Feb., v. 15, No. 2, 35–49, 6 figs. [27 refs.]

The authors review the literature on mycetoma in the United States and Canada, and give an analytical table of 38 cases. Three new cases are described, which occurred in Louisiana in 1936, 1940 and 1944 respectively. In the earlier two cases the infecting fungi were of the black-grain variety and, although they had not been identified mycologically at the time of writing the paper, the descriptions given suggest that both belong to the genus *Madurella*. In both cases there was some destruction of the bones of the tarsus and metatarsus as well as of the soft tissues. One case was of special interest because an interval of 18 years elapsed between the presumed time of infection, through penetration of the foot by a long pinewood splinter, and the onset of signs of mycetoma. The

other case presented the unusual feature of an associated large inguinal bubo ; although it is not stated that this was due to metastasis of the fungus. The third case was of the yellow-grain variety and, apparently, the lesion was less severe than in the other two cases, for although they had to be treated by amputation of the foot, this patient was put on " medical " treatment. The fungal hyphae seen in the parasitic " grain " are said to have measured 2 to 5μ in diameter, but " an organism believed to be *Actinomyces* was isolated from the grains and will be reported on later." Cultures of this apparent *Actinomyces* were inoculated into rabbits, guineapigs and mice, but the results of these experiments were inconclusive, and no progressive lesion was caused.

J. T. Duncan.

Binford, C. H. & Lane, J. D. **Actinomycosis due to** *Nocardia asteroides*. **Report of a Case.** *Amer. J. Clin. Path.* 1945, Jan., v. 15, No. 1, 17–23, 5 figs.

The first recorded case of infection by *Nocardia asteroides* (syn. *Actinomyces asteroides*), was that described by Eppinger in 1890, in which this acid-fast microorganism caused abscesses and pseudotuberculous granulomata in the brain and lungs. Following Eppinger's case, a number of other cases of infection by the acid-fast type of " *Actinomyces* " has been reported, and the species has usually been named *asteroides*. In several of these cases the lungs, and less frequently the brain and meninges, have been affected. In the new case reported by Binford and Lane the patient, a man aged 51, suffered from an attack of " influenza " accompanied by " numbness of the forehead." Two months later a convulsive seizure occurred, which was followed by hemiplegia with aphasia. An ischio-rectal abscess also developed and the patient died nine weeks after the first symptoms were noticed. At autopsy a patch of pulmonary consolidation, containing several small abscess cavities with great thickening of the overlying pleura, was found. The left cerebral hemisphere contained one abscess 6 cm. in diameter, and two smaller abscesses. Smears of pus from the brain, lung and ischio-rectal abscesses showed " numerous filaments of slender (0·2–0·5 microns) Gram positive, irregularly acid-fast, non-septate, branched mycelium," and the organism was isolated in culture. Rabbits inoculated with 0·1 cc. of a broth culture of the fungus died from a generalized infection in 48 hours, and guineapigs given 1·0 cc. of the same culture into the peritoneum died within twelve days. The disseminated lesions in these animals were not pseudotuberculous, but were necrotizing miliary abscesses in which the acid-fast fungus was seen. After two years' cultivation in the laboratory the fungus, which had been identified as " *Nocardia asteroides* (Eppinger) Blanchard," was found to be still virulent for animals.

J. T. Duncan.

Watrin, J. & Surdey. Blastomycose cutanée à foyers multiples. [**Multiple Cutaneous Blastomycosis.**] *Semaine des Hôpitaux de Paris.* 1946, Feb. 21, v. 22, No. 7, 280–83, 5 figs.

Taiana, J. A., Boragina, R. C. & Niño, F. Granuloma paracoccidioidico. Laringobroncoscopia en dos casos. [**Paracoccidioidal Granuloma. Laryngobronchoscopy on Two Cases.**] *Rev. Asoc. Med. Argentina.* 1945, Dec. 15, v. 59, No. 571, 1356–60, 10 figs. [32 refs.]

Paracoccidioidal granuloma is mycologically more closely related to North American blastomycosis (Gilchrist's disease) than to coccidioidal granuloma. Although the disease affects chiefly the skin, the viscera and the lymphatic glands, the authors believe that the initial lesion usually occurs in the mouth as

an ulceration of the mucosa on the cheek, tongue, tonsils or pharynx, and from these sites the infection spreads, by the lymphatics, to the viscera and the skin. The diagnosis depends upon the identification of the fungus, *Paracoccidioides brasiliensis*, in microscopical preparations from the lesions, and in culture. The value of the laryngoscope and bronchoscope was proved in two cases in the authors' clinic: by this means nodular and ulcerative lesions on the larynx and vocal cords were seen, and specimens were obtained by biopsy for examination. The evidence obtained by bronchoscopy confirmed the view that pulmonary involvement in this disease is fairly frequent. X-ray examination of the chest was more useful in following the progress of the disease than in diagnosis.

In both cases described in the paper there was extensive disease of the mouth parts and the larynx, with involvement of the lungs and the lymphatic system, but both recovered, despite relapses, under intensive treatment with drugs of the sulphonamide group. *J. T. Duncan.*

Lacaz, C. da S. Contribuição brasileira para o estudo da blastomicose sul-americana (granulomatose paracoccidióidica). [**Paracoccidioidal Granuloma in Brazil.**] *Hospital.* Rio de Janeiro. 1945, Aug., v. 28, No. 2, 249–60.

Woodruff, E. & Castellanos, L. **Histoplasmosis.** *Rev. Mexicana de Tuberculosis.* 1945, July–Aug., v. 7, No. 37, 215–20. [English version 221–7.] [15 refs.]

A general account.

HEAT STROKE AND ALLIED CONDITIONS.

Stenning, J. C. **Salt Deficiency States in Tropical Climates.** *J. Roy. Nav. Med. Serv.* 1945, July & Oct., v. 31, Nos. 3 & 4, 129–46; 195–211. [16 refs.]

During 2½ years of service in tropical waters, the author saw on his ship many cases of sub-clinical salt deficiency, associated with dizziness, lack of concentration, etc. [compare Saphir, this *Bulletin*, 1946, v. 43, 377], and 120 clinical cases, all attributable, in his opinion, to salt deficiency. The sub-clinical symptoms were all promptly relieved by increasing the daily salt intake, estimated by Stenning to have been initially about 10 gm. per day. Salt deficiency was judged in all instances by arbitrary standards, which are not given, but few patients had less than 0·2 per cent. sodium chloride in their urine; in a few cases plasma chloride levels were estimated, and in these the degree of diminution in the plasma was directly proportional to the degree of diminution in the urine [a relationship not invariably found by others]. Twenty-four-hour urine volumes and specific gravities are not recorded. The men were exposed to conditions varying from hot-dry (140°F. with relative humidity 14 per cent.) to hot-wet (102°F., with relative humidity 83 per cent.); air movements were usually low. Stenning considers that when the daily urinary chloride ouput is less than 3 gm. (as sodium chloride) symptoms may occur.

Most of the clinical cases described were of the well-known type, showing peripheral circulatory failure, low body temperature, cramps of varying severity and gastrointestinal symptoms. Not all the symptoms were present to the same intensity throughout the group, and Stenning puts forward a detailed sub-classification based on the predominant one. Some cases with severe abdominal symptoms were mistaken for abdominal emergencies

and subjected to laparotomy [other instances where this has happened are known to the reviewer]. The patients were usually given saline intravenously (2 per cent. or even 5 per cent. was suggested for some cases) and, later, fluids and salt by mouth; they recovered in a few days. Many cases were in men who had scorned to take extra salt [no patient showed extreme salt deficiency *i.e.* the urine always contained some chloride].

Two types of pyrexial case are also described. In one there was profuse vomiting, followed by diarrhoea and a rising body temperature up to 103·5°F. associated with a dry skin. In the case of this type cited, salt deficiency was not really shown. The other type of pyrexial case had a higher body temperature, but no vomiting and no diarrhoea. In both types of case, prompt mechanical cooling was the treatment of choice. The author contends that the hyperpyrexia and incipient hyperpyrexia in these instances were both manifestations of salt deficiency, but he fails to bring forward adequate evidence. [The author's preoccupation with salt deficiency as the universal cause of all heat disease leads him to ignore other possible causes, *e.g.*, endocrine or nervous.] *W. S. S. Ladell.*

MISCELLANEOUS DISEASES.

PAVILLARD, S. S. **Medical Experiences in Siam.** [Abridged.] *Brit. Med. J.* 1946, Jan. 26, 135–7.

This is a dispassionate account of typical conditions experienced by military prisoners of war engaged in road and railway construction in Siam during the period April 1942 to August 1945.

The author describes one of the worst of the early camps in Singapore. In this camp there were no latrines, the washing and cooking facilities were quite inadequate, the men were crowded into bug-infested huts, and became infested with lice. They were employed as labourers, but were given so poor a diet that many of them developed beriberi or pellagra. These conditions prevailed throughout captivity, and any great exertion or fatigue "invariably led to an outbreak of beriberi and pellagra." At this camp, diphtheria was prevalent, and many of the men contracted diphtheritic infection of the scrotum, previously the site of pellagroid dermatitis. The dysenteries, particularly the bacillary form, were widespread.

The railway journey to Siam was made in covered goods wagons—32 men to a truck—without even the most primitive sanitary arrangements on the train. The camp to which the men were directed was in a flooded rice field; the "hospital" hut was flooded to a depth of 2 ft., the water was full of mosquito larvae, and there were many cases of malaria. The march from this camp into the jungle is described. Many men suffered from heat exhaustion and cramps due to loss of salt by sweating; the only water available was that in roadside wells and pools, which could not be chlorinated. Throughout, no shelter from the heavy rain was provided at night, the only food was rice, and the exhaustion of the men, after continuous marching through mud, was so great that they could continue only if given a day of rest.

The destination of these men was a camp at Wampo, where they remained for 7 months, during which they built a section of the railway. This camp eventually held 1,500 men, most of whom could not be accommodated in the two huts available. On a diet of plain rice, syncopal attacks and gastro-intestinal disorders were common. Malaria was rife and at first no quinine was available; later, a five-day course of quinine, 9 grains daily, was all that could be given. The prisoners gradually improved the camp, with the result

that the rate of sickness declined. Of 1,500 men, 15 died in 7 months, a proportion which compared favourably with the monthly death roll of 60–120 in neighbouring camps. Local purchase of food (rice-polishings and meat) and drugs was allowed; prices were very high.

At this time the main diseases were malaria, beriberi, tropical ulcer and dysentery (amoebic increasing and bacillary decreasing). Shortage of specific drugs presented a difficult problem when it came to deciding to whom they were to be given. Diphtheria occurred, but in spite of the fact that no antitoxin could be obtained, there were only two deaths in 20 cases; in some of these cases Vincent's infection was probably also present.

Later the Japanese abolished the weekly half-day rest, and the men were given no chance to wash or air their clothes. Scabies, ringworm and other skin affections were rife; the huts were heavily infested with bugs and lice; scrub typhus, beriberi, pellagra, malaria, the dysenteries and tropical ulcers were becoming increasingly common. The Japanese, however, began to issue pay to the prisoners, who all subscribed to a central pool for purchase of supplementary food and drugs; rice-polishings were bought and issued each day; with the result that there was a marked decrease in the incidence of beriberi.

Later, the battalion moved into an area in which cholera was prevalent, but the men (who were mostly educated) had previously been warned by the author, and instructed how best to prevent infection, with the result that only seven died, whereas other units lost up to 50 per cent. of their strength. The Japanese commander, a non-commissioned officer, refused to permit the organization of a sanitary squad big enough to cope with the situation, or to allow water to be drawn from the river above the point at which the coolie labour force contaminated it. The coolies themselves were badly affected by the epidemic, and large numbers died; they were allowed no medical attention, and were given neither food nor water, except that which the British orderlies surreptitiously passed to them. The dead were buried in pits, necessarily dug much too close to the camp because there were not enough men to clear the jungle. [In many other camps the dead were "cremated."] The author had already constructed a small plant for the distillation of water for intravenous salines, and this form of treatment was used during the outbreak, together with the oral administration of potassium permanganate (3 grains every quarter of an hour). In a few cases sulphapyridine was used, apparently with good results.

It was not surprising that after months of these appalling conditions, with more or less constant incapacitation from one or several of the prevalent diseases, and totally inadequate facilities for treatment, the more chronically sick tended to become apathetic and exhausted beyond endurance. [Persuading these men to eat was a continual difficulty.] *L. H. Turner.*

Ghosh, L. M. & Panja, D. **A Case of Rhinoscleroma.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 511, 4 figs. on 1 pl.

Harvey, A. M., Kuffler, S. W. & Tredway, J. B. **Peripheral Neuritis. Clinical and Physiological Observations on a Series of Twenty Cases of Unknown Etiology.** *Bull. Johns Hopkins Hosp.* 1945, Aug., v. 77, No. 2, 83–103, 5 figs. [13 refs.]

The condition described in this paper occurred among men of the United States forces who had served in the tropics. In 16 of the patients the common peroneal nerve was involved, in three the axillary and in one the radial. No known aetiological factor to account for the neuritis could be discovered, and there was no evidence of diphtheria or of vitamin deficiency. In the majority of the patients the condition appeared suddenly, the onset being gradual in

only four of the series. In eight of the patients there had been an attack of benign tertian malaria within eight days of the onset of the neuritis ; two had had malaria at some other time, but in the remaining ten patients there was no clinical or laboratory evidence of malaria.

In all cases the patient's complaint was of weakness of an extremity. The three men with axiliary nerve involvement and two of the others complained of severe pain. Numbness or paraesthesiae occurred in 14 of the patients. Loss of muscular power was most marked in the patients with axillary nerve lesions ; all these had complete loss of deltoid function, and in two of the three there was evidence of involvement of other nerves of the brachial plexus. Muscular weakness was not so prominent a feature in the patients with peroneal nerve involvement ; in only three of these was there much atrophy. Laboratory investigations did not help in clarifying the aetiology of the condition.

Electromyographic studies were made on the affected muscles, by stimulating the nerve trunk with condenser discharges or an induction coil, and recording the action potential in the muscles by cathode ray oscillograph. It was found by this method that the voltage of the action potential of the affected muscles was less than normal. The amount of reduction of voltage was proportional to the muscular weakness as assessed clinically. When a second stimulus was induced at a short interval after the first, the affected muscle responded in a manner similar to a normal muscle ; there was no evidence of a summation of impulses at the neuromuscular junction. It was thought these facts indicated that the nerve fibres which were affected were completely inactive, surviving fibres functioning normally, and that there was no defect of muscle fibres. A tetanic stimulation did not produce a myasthenic response, nor did prostigmine alter the character of the muscular contraction.

Treatment consisted in rest, the prevention of stretching of the affected muscles, and graduated exercise. The radial palsy and, with one exception, the peroneal palsies all improved slowly to satisfactory recovery, but the axillary palsies did not recover while under observation. The authors concluded that the neuritis could not be connected with the antimalarial suppressive treatment with quinine and atabrine which all the patients had had. Nor was there any evidence in favour of a vitamin deficiency.

The possible relationship between the condition described and malaria is discussed. The type of neuritis which the authors found in association with malaria presented as polyneuritis with pain and heightened muscle tone, whereas the patients in this series complained of weakness in muscles supplied by a single or a few nerves, pain was not consistent and muscle tone was poor. It is concluded that malaria was not primarily responsible, but might have been a precipitating factor. The literature is reviewed and attention is drawn to the reports of similar cases made by SPILLANE and by WYBURN-MASON. The paper ends with the case histories of two patients who presented typical signs and symptoms.

[This is yet another report on a series of cases of a type of neuritis which is receiving increasingly more attention in the medical press. One would have welcomed information as to whether any of the patients had received prophylactic or therapeutic serum injections.] *W. Tegner.*

VAN DEN BERGHE, L. Syndrome thrombopénique ou onyalai. Observation d'un cas provenant du Congo Belge. [**Thrombocytopenia, or Onyalai, in a Patient in the Belgian Congo.**] *Ann. Soc. Belge de Méd. Trop.* 1945, June 30, v. 25, Nos. 1/2, 49–55.

The importance of this case lies in the facts that the patient was a European and that his history of symptoms prior to those characteristic of onyalai were

peculiar. After a journey of three months in the bush the patient, in September 1938, complained of feeling tired and consulted a doctor, who could find nothing definite; the man therefore continued on his way. Soon afterwards he felt severe pain in the left wrist, which became swollen, and the following day the right wrist swelled in the same manner. After the application of hot compresses for three days these symptoms disappeared; the right shoulder was then affected but cleared up on similar treatment after a week. Eight days later the left knee swelled and was so painful as to prevent sleep, but he continued at work and the condition cleared up in eight days. Some time later he felt "discomfort in the teeth" and small bullae appeared at the base of the lower incisors; he noticed that he was becoming jaundiced. In January 1939 he complained of dryness of the throat and difficulty in swallowing, followed by an acute pharyngitis with marked swelling, and for four days he could swallow nothing. Gargles and inhalations gave relief, but haemorrhage from the mouth and gums supervened and the jaundice increased. While being examined by the doctor he had a fainting attack followed by coughing or vomiting of blood [it was not decided which]. Thereafter he had frequent bleedings from his gums and spat up blood; slight exertion caused much shortness of breath. He went into hospital towards the end of February and a blood examination yielded the following information: red cells 800,000, leucocytes 3,600, thrombocytes 5,600 per cmm., haemoglobin 27 per cent., colour index 1·6; erythroblasts numerous. He was seen by a specialist, a cardiologist, who prescribed salicylates, which made him worse; red cells fell to 600,000, white 2,000 per cmm., haemoglobin 15 per cent. He was then given blood transfusions, without much improvement till some 20 had been given, when the red cells reached 4 million. More transfusions of 250 cc. were given on alternate days and the red corpuscles rose to 4,700,000, the white cells to 4,600 per cmm., and the haemoglobin to 99 per cent. Thrombocytes now were 80,000. He was kept under observation and was seen every three months for four years and remained well. In 1944 he was killed fighting in the great war.

The causation is considered but no conclusion is arrived at. It is suggested that insect bites might have injected some hypothetical virus, or that as, on his journeys, he often had to push his motorcycle for considerable distances his head would then be near the petrol tank and he may have been poisoned by inhalation of petrol fumes. *H. Harold Scott.*

SHOURIE, K. L. **An Outbreak of Lathyrism in Central India.** *Indian J. Med. Res.* 1945, Oct., v. 33, No. 2, 239–47. [15 refs.]

The outbreak studied by the author occurred in the eastern part of Bhopal State, Central India. At least 1,200 are said to have been attacked; he examined some 150 and studied more closely about half that number. Most of these were in the second and third decades of life and males preponderated over females in a proportion of 7 or 8 to one. Of 69 cases specially noted, 56 occurred during the three months August–October, the figures being 11, 23 and 22, respectively. There is nothing particular regarding the symptoms; they were typical. Those attacked were of the poorer classes. For the past 2–3 years the crops have been bad and damaged by rust, blight, bad weather, etc., and the people have mixed cheaper grains in increasing amounts with the wheat, and for some months—six or more—had been consuming large quantities of *Lathyrus sativus*. Examination did not discover any admixture with *Vicia sativa*.

Lathyrus can be consumed in small or even moderate quantity with impunity, but when it has to be used almost exclusively for six months or so, danger is imminent. The obvious remedies are to provide alternative crops and improve

the condition, status and earning power of the agricultural labourer. In the words of the author, " prevention is a social, economic, administrative and agricultural problem." *H. Harold Scott.*

MERSKY, C. **A Case of Stinkblaar (*Datura stramonium* L.) Poisoning associated with Hyperpyrexia.** *Clin. Proc.* Cape Town. 1945, Nov., v. 4, No. 9, 509–12.

[See this *Bulletin*, 1945, v. 42, 497, 498.]

FRACHTMAN, H. J. & MCCOLLUM, W. T. **Portuguese Man-of-War Stings: a Case Report.** *Amer. J. Trop. Med.* 1945, Nov., v. 25, No. 6, 499–500.

A sailor, aged 23, when swimming was stung on his arms and thighs by a " Portuguese man-of-war " (the jelly-fish *Physalia pelagica*). An hour and a half later he was nauseated and soon afterwards began to have spasms of the abdominal muscles. His temperature on admission to hospital was only 98·6°F., but the pulse was 96 and respirations 24 per minute and he was " very apprehensive." Little or nothing abnormal was discovered by blood examination ; red corpuscles were 4½ million ; leucocytes 11,500 per cmm. ; haemoglobin 14·9 gm., and the differential leucocyte count normal. Red lines, not raised, were visible over the front of the right thigh and shoulder. In spite of the spasms of the abdominal muscles and diaphragm there was little if any respiratory distress, but the muscular contractures became more severe and spread to the neck, arms and legs, with muscular pain. External stimuli, such as bright lights, jarring of the bed, or sudden noises precipitated the attacks ; the mind remained clear. Ten hours later, respiration was slow and laboured, interrupted by diaphragmatic spasms, but *there was no cyanosis and the temperature, pulse, and blood pressure were within normal limits* [our italics]. On the next two days the patient was better in the mornings, but the symptoms returned later in the day ; during the next five days the spasms gradually diminished and on the sixth had ceased altogether and recovery was complete and uninterrupted.

[The patient was said to be a " well-adjusted individual who had no abnormal psychoneurotic tendencies " but he was " very apprehensive " and the fact of respiratory distress without cyanosis or change in pulse rate is much in favour of a hysterical element being present. Nothing is said of the pain and numbness which are usually present in stings by *Physalia*, but a choking sensation, dysphagia and dyspnoea are common, together with spasm of the abdominal muscles. This case is perhaps peculiar in the prominence of the last-named symptom.] *H. Harold Scott.*

GENERAL ENTOMOLOGY.

KNIPLING, E. F. **The Development and Use of DDT for the Control of Mosquitoes.** *J. National Malaria Soc.* Tallahassee, Fla. 1945, June, v. 4, No. 2, 77–92. [23 refs.]

At the laboratory of the Bureau of Entomology and Plant Quarantine in Florida, U.S.A., investigations into the uses of DDT for mosquito control began in October 1942. In this paper the author briefly summarizes and in some cases discusses a number of the tests made in the laboratory and in the field against larvae and adults of the following anophelines and culicines : *Anopheles quadrimaculatus*, *Anopheles albimanus*, *Anopheles crucians*, *Culex quinquefasciatus* [*C. fatigans*], *Aëdes aegypti*, and *Aëdes taeniorhynchus*.

Using fourth-stage larvae of *A. quadrimaculatus* in the laboratory it was shown that a colloidal suspension of one part of DDT in 100 million parts of water produced complete mortality in 48 hours. Similar results were obtained with aqueous emulsions. Experiments with dusts showed that DDT was 25 times as toxic as paris green. Petroleum-oil solutions were as effective per unit of toxicant as dusts or suspensions.

Adults of *Anopheles quadrimaculatus* and *Aëdes aegypti* were used in laboratory tests of DDT in residual sprays. The latter species was slightly more susceptible than the former. Aerosols were shown to be as effective as finely atomized sprays, though from a practical standpoint the sprays have several advantages such as economy in application, transport and cost.

In the field, natural breeding places were treated with DDT in dust, oil solutions, aqueous emulsions, liquefied gas aerosols and smokes applied with different types of equipment. The use of aircraft for distributing sprays produced favourable results against adult salt-marsh and other mosquitoes as well as against their larvae.

Many figures relating to these experiments are discussed in the text and some of them are given in eight tables, all emphasizing the far-reaching importance of DDT in mosquito-control operations. *H. S. Leeson.*

Blakeslee, E. B. **DDT Surface Sprays for Control of Stablefly Breeding in Shore Deposits of Marine Grass.** *J. Econom. Entom.* 1945, Oct., v. 38, No. 5, 548–52.

Smith, C. N. & Gouck, H. K. **DDT to control Ticks on Vegetation.** *J. Econom. Entom.* 1945, Oct., v. 38, No. 5, 553–5.

Vanderplank, F. L. **Insecticidal Properties of *Euphorbia* Extracts.** [Correspondence.] *Nature.* 1945, Dec. 29, 782.

Varying results were obtained in trials of extracts of *Euphorbia tirucalli* as insecticides; the author found that aqueous extracts of fresh branches had no effect on mosquito larvae but they "seemed to have some insecticidal effect on adult Diptera." An extract of young shoots (previously dried in an oven at 100° C.) in 100 cc. of kerosene "gave 100 per cent. kill of adult Glossina and other Diptera" [used both as a spray and as a contact poison (personal communication)]. On the other hand, the Industrial Research Board, Nairobi, Kenya, found that extracts made according to the author's formula had no appreciable insecticidal properties. On repeating his tests the author got the same results as previously but extracts prepared from sun-dried shoots had no appreciable insecticidal properties. Owing to pressure of work the investigation was stopped.

An experiment seemed to show that this plant will protect young vegetables against grasshoppers, slugs, snails and other insects. [See also this *Bulletin*, 1945, v. 42, 502.] *J. F. Corson.*

Lauterburg-Bonjour, M. Ueber einen Fall von Myiasis durch eine Hypodermalarve. [**A Case of Myiasis due to a Larva of *Hypoderma*.**] *Schweiz. med. Woch.* 1946, Mar. 2, v. 76, No. 9, 168–70.

Smart, J. **The Classification of the Simuliidae (Diptera).** *Trans. Roy. Entom. Soc. London.* 1945, Dec. 31, v. 95, Pt. 8, 463–532. [Numerous refs.]

The author gives us a full account of views which have been held as to the classification of the Simuliidae. He adds his own conclusions.

The family Simuliidae is sharply separable from other Diptera and appears to have no close relation with other families. The family is divided into the

Parasimuliinae (which contains only *Parasimulium*), and the Simuliinae (containing five genera, *Cnephia*, *Austrosimulium*, *Gigantodax*, *Prosimulium* and *Simulium*). These genera are discussed fully, and a key is given for their separation.

The paper contains a catalogue of all specific names which have been used for Simuliidae. Of these there are 800 (but this does not imply the existence of 800 known species). *P. A. Buxton.*

LABORATORY PROCEDURES.

MANWELL, R. D. **The J.S.B. Stain for Blood Parasites.** *J. Lab. & Clin. Med.* 1945, Dec., v. 30, No. 12, 1078–82, 1 fig.

" The J.S.B. stain, recently introduced by Singh and Bhattacharji, has been tested and been found superior in most respects to any of the other commonly used processes for the staining of blood and blood protozoa. The technique is simple and the staining process can be completed in less than two minutes for thin smears and in less than one minute for thick films. The staining solutions are not difficult to make up, are relatively inexpensive, and keep well for weeks or months, even in hot weather. Preparations stained by this process appear very much like those made by Giemsa's method, cytoplasm and chromatin of blood cells and parasites being differentiated with equal clearness and having similar color values. J.S.B. preparations are somewhat less resistant to fading but will stand much more exposure to light than they would ordinarily receive." [See this *Bulletin*, 1944, v. 41, 822.]

REDDY, D. G. & THANGAVELU, M. **A New Technique in Sternal Puncture.** *Indian Med. Gaz.* 1945, Oct., v. 80, No. 10, 502–4, 5 figs. (2 on 1 pl.) [13 refs.]

Reddy has devised a sternal puncture needle which will remove marrow without abnormal admixture of blood because there is no aspiration. It is a steel rod with a stout handle, the rod being 2 in. long, of ·44 gauge, the terminal ¾ in. having a deep longitudinal groove, one edge of which is sharp and projects more than the other ; the point is bevelled. When the needle is rotated clock-

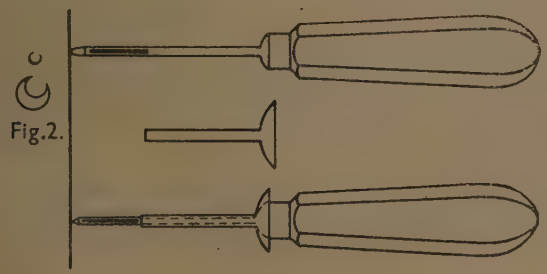


Fig. 1.—Reddy's sternal puncture needle with the shield.
Fig. 2.—Section of the needle across the gutter, lower one magnified.
[Reproduced from *Indian Medical Gazette*.]

wise in the marrow the sharp edge cuts the marrow so that the groove is filled. A cannula fits over the rod in its upper part between the proximal end of the groove and the handle.

The point is made to enter the bone vertically, then the handle is depressed to an angle of 30° to the surface of the sternum and the rod is pushed into the marrow for 1 cm.; it is then rotated clockwise for one or two turns and withdrawn, the cannula preventing the soft tissues from displacing the marrow from the groove. Satisfactory smears can be made, the cell counts being more accurate than in smears of marrow obtained by aspiration where dilution with blood occurs [see also MERTENS, this *Bulletin*, 1946, v. 43, 257].

J. F. Corson.

SUÁREZ, R. M., DÍAZ RIVERA, R. S. & HERNÁNDEZ MORALES, F. **Hematological Studies in Normal Rhesus Monkeys** (*Macaca mulatta*). **1. Venous Blood Studies. 2. Bone Marrow Studies.** *Puerto Rico J. Pub. Health & Trop. Med.* 1942, Dec., v. 18, No. 2, 212–26, 1 pl. [Refs. in footnotes.] [Spanish version 227–41.]

Being struck by the scarcity of publications dealing with the cell content of normal monkey blood and the complete lack of information regarding the cells of the bone marrow, the authors decided to study the blood and bone marrow in normal rhesus monkeys of various ages. The blood was obtained from a peripheral vein in 38, while the bone-marrow was aspirated from the sternum of 40. The general results of the study of this material are given in the summary to the paper, which is as follows :—

" 1. Hemoglobin estimations for 38 Rhesus monkeys were as follows: infant monkeys, 84·62 per cent.; young, 90·5 per cent.; adult, 91·16 per cent., with ranges of 76 to 94, 80 to 110, and 76 to 117 per cent., respectively.

" 2. Red blood cell count averaged 4,197,500 in the infant, 5,172,500 in the young, and 5,235,000 in the adult animal.

" 3. Platelet count averaged over 300,000.

" 4. Reticulocyte counts were 2·9 per cent. for infant, 1·85 per cent. for young, and 1·58 per cent. for the adult animals.

" 5. The average total leukocyte count was 15·107 for infant, 17,562 for young, and 9,999 for the adult animals.

" 6. Metamyelocytes averaged 0·75 per cent. in the infant, 0·5 in the young, and 1·15 in the adult animals.

" 7. Neutrophils were more abundant in the venous blood of the adult than in that of the young or infant monkeys, the average for the infant being 36·12 per cent., for the young, 38 per cent. and for the adult, 50·25 per cent.

" 8. Eosinophilia was quite pronounced in the young and adult monkeys, which may be attributed to intestinal parasitism. Averages of 3·06 were found for infant animals, 4 per cent. for young, and 4·92 for adult.

" 9. Lymphocytes were found in higher percentages in both infant and young animals than in adult, such percentages being above 40 in all the series analyzed. Averages were given of 57·75 for the infant, 56·75 for the young, and 42·19 for the adult animals.

" 10. It was the authors' impression that there is a relative proportion of different blood elements in the monkey comparable to those of the human infant and young; however, these differed slightly from the venous blood of the adult human.

" 11. Morphologically, the neutrophils and eosinophils appeared to have multiple lobulations in their nuclei; sometimes as many as thirteen to fourteen lobes were counted in one cell. The lymphocytes appeared to be larger than in human blood and, in many cases, coarsely granulated.

" The following results were obtained among the forty Macacus submitted to bone marrow aspirations :

" 1. The average erythrocytic series in the infant was higher than in either the young or the adult animal.

" 2. The average granulocytic series was higher in the adult than in either the infant or young, the young animal's marrow being richer in those cells than the infant's.

" 3. The young monkey had more erythrocytic cells in its marrow than the adult.

" 4. Lymphocytes were more numerous in the infant and the young than in the adult monkey.

" 5. Ratios for erythrocytic and granulocytic components were as follows : infant, 1 : 2·8 ; young, 1 : 3 ; adult, 1 : 4.

" 6. Morphologically, the cells of the bone marrow resembled those of humans, except for the multiple lobulations of the nuclei of the polymorphonuclear leukocytes and for the larger size of the lymphocytes of the animal.

" 7. Megakariocytes were seen in very low percentages, 0·2 in only two adult animals. None were seen in either young or infant monkeys.

" 8. If it were not for the high number of lymphocytes, the bone marrow of the monkey would approach the human picture at different life stages."

C. M. Wenyon.

REPORTS, SURVEYS AND MISCELLANEOUS PAPERS.

WENYON, C. M. **Tropical Medicine in War and Peace.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1945, Dec., v. 39, No. 3, 178–94.

This presidential address refers to the stimulus provided by the two world wars, to research into the possibilities of improving methods of safeguarding the health of troops in tropical and sub-tropical countries. Very noteworthy contributions to tropical medicine were made in both. During the 1914–18 war LEIPER worked out the life-history of *Schistosoma haematobium* and *S. mansoni*. Important additions to our knowledge of the dysenteries were made. Weil's disease was intensively studied. The louse was incriminated as the vector of European typhus fever, and the Weil-Felix reaction was elaborated. The limitations of quinine in the treatment of malaria were more clearly defined as a result of war experience.

The second world war has been even more productive of new knowledge than the first. Most important of all perhaps is the knowledge of what atebrin can do to prevent clinical malaria among troops operating in hyperendemic malaria country. The important work of FAIRLEY and his colleagues at Cairns in Australia is strongly suggestive of the existence of an exoerythrocytic cycle of development of the human malaria parasite. The discovery of the remarkable insecticidal properties of DDT is of great and far-reaching importance. Insect repellents have been discovered—dimethyl, diethyl, and dibutyl phthalates—which do what is claimed for them. A vaccine against scrub-typhus (tsutsugamushi disease) has been prepared and used, but the results have not yet been reported. Against louse-borne typhus a formalinized rickettsia vaccine, prepared from egg yolk cultures, has been widely used, and it is believed that some degree of protection was afforded, but DDT has given the most remarkable results in the prevention of typhus fever. A shirt impregnated with DDT retains its insecticidal properties throughout a number of launderings. In the treatment of bacillary dysentery, sulphaguanidine has

been used with most satisfactory results, and it is possible that other sulphonamides may be even more effective. In amoebic dysentery cases that are resistant to anti-amoebic remedies marked clinical improvement may follow the administration of penicillin but without eliminating amoebae; after this improvement the amoebic infection may become amenable to specific treatment. The war years also saw the final proof that kala azar in India is transmitted by *Phlebotomus argentipes*. Russian investigations in Middle Asia showed that a gerbil, *Rhombombys opimus*, is the reservoir of the leishmania of oriental sore, which is transmitted to man by *Phlebotomus papatasi*, another sandfly, *P. caucasicus*, being responsible for maintaining the rodent infection in the burrows. Such are the outstanding achievements of tropical medicine during these last war years.

The address then dealt with the future of tropical medicine, and with the present state of tropical medicine in Great Britain. At present the facilities for giving instruction in tropical medicine in London, as well as for the study of tropical diseases and their treatment, are sadly deficient. A very strong case is made out for the early creation in London, the centre of an Empire with vast tropical responsibilities, of a Tropical Medicine Centre which would combine a hospital for tropical diseases and a school of tropical medicine. This " would restore the position formerly held by this country, would be a monument to the many pioneers who devoted themselves to the study of tropical disease and would be a centre of tropical medical activity worthy of the British Empire."

Norman White.

i. ALLAN, P. **The Progress of Public Health Work in the Native Territories.** *South African Med. J.* 1945, Nov. 10, v. 19, No. 21, 402.

ii. MEARS, A. R. R. **The Part-Time District Surgeon in the Transkeian Territories.** *Ibid.* 402–5.

iii. DE VILLIERS, V. M. **Rehabilitation of the Transkei.** *Ibid.* 405–6.

iv. HUBBARD, C. S. **Afforestation and Fuel Supply in relation to Development in the Transkeian Territories.** *Ibid.* 407–8.

v. DREWE, F. **Some of the Problems of Leprosy.** *Ibid.* 408–10. [11 refs.]

vi. FRASER-SHEARER, W. **Transkeian Memories.** *Ibid.* 410–12.

vii. SOUTH AFRICAN MED. J. 1945, Nov. 10, v. 19, No. 21, 412–14. **Educational Aspects of the National Feeding Scheme.**

viii. ZONDO, W. T. **The Training of Bantu Women Community Workers at the Mbuto Training Centre, Tsolo.** *South African Med. J.* 1945, Nov. 10, v. 19, No. 21, 414.

ix. SOUTH AFRICAN MED. J. 1945, Nov. 10, v. 19, No. 21, 415–17, 1 map. **Medical Services : Transkeian Territories, 1945.**

x. SOUTH AFRICAN MED. J. 1945, Nov. 10, v. 19, No. 21, 418. **Vacation Courses for Medical Students in the Transkei.**

xi. ELDER, J. H. **Jeanes Teachers.** *South African Med. J.* 1945, Nov. 10, v. 19, No. 21, 419–20.

i. In the introduction to this series of papers Allan remarks that there is now much more movement into and out of the Native Territories of South Africa than was the case 25 years ago, and that this movement has entailed much spread of disease and much change in mode of life. During the last 4 years a concerted attempt has been made to deal with these diseases, and the work will be continued.

ii. The paper by Mears is largely concerned with the official duties and private practice of the District Surgeons. He discusses certain grievances, but from the point of view of readers of this *Bulletin*, the important part of the paper is that in which it is stated that in the Transkei there are 1,281,823

Africans, 17,598 Europeans and 10,000 Coloured ; for this population there are 13 hospitals (8 of which are mission hospitals) with 607 beds, and about 50 doctors.

iii. De Villiers refers to the basic reasons for the deterioration of agriculture and health in the Transkei which, for many years, has been a matter for concern. The land has become seriously eroded and denuded as a result of overstocking and inefficient farming, there has been a steady deterioration in the quality of cattle, and a shortage of milk for human consumption. The result has been serious malnutrition and heavy infant mortality. [The general position was set out in the series of papers reviewed in this *Bulletin*, 1943, v. 40, 865.] Plans have now been made, and work started, to improve the general agricultural position. The project is very big, but not too big for the problem ; it entails much engineering construction work, afforestation, agricultural supervision and education, and introduction of new stock with restriction of the old. It is a programme which will affect health, chiefly because it is directed against the fundamental causes of ill-health, malnutrition and ignorance. Already a useful amount of work has been done.

iv. Hubbard takes up the subject of afforestation and fuel supply, showing that at present the wood taken for fuel is much below even a reasonable minimum ; yet because this wood is scarce the people burn farm manure and mealie stalks which are needed to fertilize the land. Moreover, timber is an essential for construction purposes in any health or industrial programme. The proper degree of afforestation is therefore important for health, and the balance between the use of land for this purpose and for agriculture must be worked out with care.

v. Drewe discusses leprosy as he has seen it at the Holy Cross Mission Hospital. Many of his points have already been noticed in this *Bulletin*, 1945, v. 42, 292.

vi. The paper by Fraser-Shearer is well described by its title ; those who have practised surgery in Africa will recall cases, similar to those he describes, of the immense resistance to shock and infection exhibited by the Africans. He makes one point of public health importance, however, in his remarks on the senile patient with chronic pulmonary tuberculosis and positive sputum, who lives with his family during his slow decline, and infects the younger members. " If we trouble to elicit his family history, we find in 80 per cent. of cases that the patient's children, and even grandchildren, have died in numbers in their early teens of acute miliary tuberculosis." The building of hospitals for the acute cases in contacts seems futile while the source of infection is allowed to remain at home and to continue to infect others. The author suggests some form of segregation on farm colony lines for these chronic cases.

vii. The author of this paper, Mr. J. H. Dugard, is an Inspector of Schools, but he writes with authority, for the administration of school-feeding has been delegated to the Education Department. He points out that there is an obvious correlation between low income and malnutrition, but also that ignorance of dietary factors often produces malnutrition even when the income is satisfactory. In most families in the Transkei the schoolchildren receive only one meal each day—on their return from school—and such children are suffering from starvation, not mere malnutrition. It is to provide such children with enough food to prevent starvation that school meals are arranged. The author remarks that " in the interest of national welfare collective action to prevent human deterioration is necessary by means of a well-designed feeding scheme for children." [National welfare is, of course, important, but it would fit in with the ideals of medical men if equal stress were laid on the fact that starvation, or any other adverse condition, must be prevented in the interest of the child as an individual, who is not responsible for his own environment

and who should not, therefore, be penalized for it.] School-feeding is still in the experimental stage in South Africa, and the composition of the meals is not always good. The allowance of 2d. per meal is not ungenerous, and at that price the diet designed by Dr. S. KARK at Polela is good, but there is in some places too great a tendency to supply " bread and jam, condensed milk, pork of dubious quality, and mealie-meal with monotonous regularity instead of making determined attempts to procure protective foods." School meals should be regarded as breakfasts, and should be given as early in the day as possible.

viii. The training to which the author refers consists of one year, during which time women of approved capacity are given instruction in domestic, agricultural and medical subjects before they go to work among the African communities.

ix. In a table of facts about the Transkei it is stated, among other things, that between 80,000 and 100,000 Natives leave the Transkei each year to seek work on the mines or in other industrial centres ; 28 per cent. of families have neither cattle nor land. Smallpox was prevalent during 1945, but typhus was less in evidence than during 1944, perhaps because the outbreak of that year left a residual immunity. Approximately 100–200 persons with tuberculosis are repatriated from the mines each year.

x. This short note contains the outline of a most excellent plan by which students from the Medical Schools of the Union are given the opportunity of seeing for themselves the work carried out in the Native territories. They are " introduced to the relationship of the soil to medical practice, of the place of afforestation in the health and welfare of the people, of the relative value of pamphlets and posters and the cinema in the education of the public, and why people leave the land to seek employment in overcrowded industrial areas."

xi. Miss Elder, the head of the Jeanes Teachers Training School, All Saints' Mission, gives a short account of the function and training of these African teachers, in which she refers to the Jeanes School at Kabete in Kenya. Their name derives from Miss Jeanes, a Quaker lady of the United States, who founded the movement in the interest of better education for the Negroes. The object of these teachers is to widen the scope of school education to include training in practical domestic science, market gardening and small farming, with instruction in hygiene, elementary nursing and cooking. The evidence all points to the need for such teaching among the Africans, and to the success of the efforts so far made, but she adds :—" It seems the greatest pity that the training of these teachers has now come to an end in the Cape Province and has never been started anywhere else in the Union, for now is the time when a steady stream of such people joining the flood of workers that will be needed to rehabilitate the Transkei in the critical years to come might make a most valuable contribution to their country's welfare." A reader is left to wonder why the training of Jeanes teachers has been abandoned.

[This series of papers is important in that it gives the reader a picture of life at almost its lowest level in the people of South Africa, and in that it shows the field from which the impetus for improvement should arise. Medical men and social workers see as clearly as any others the ultimate effects of policies adopted by central governments, and it is part of their duty to make the necessary representations to governments so that these policies can be modified where change is needed. The papers also demonstrate the obvious fact that good health depends upon agriculture and education no less than on strictly medical activities. These facts are appreciated by the Government of South Africa, and if the recommendations made in the *Report of the National Health Services Commission* (U.G., No. 30–1944) are put into effect, there is every reason to believe that the situation will be radically altered for the better.

This Commission set out comprehensive schemes for personal health services (promotive, preventive, curative and rehabilitative) and non-personal health services, with the object of applying them to all sections of the population according to their need, and without regard to race, colour, means or station in life. No brief account of this long report is possible ; it is an admirable document which would serve as a basis for any scheme for comprehensive medical service in Africa, and it should be studied in detail. The authors recognize the importance of agriculture to health, but think that the function of a national health service in this respect is to advise, but not itself to embark upon, the provision of food. The report states that " the long-term policy with regard to nutrition is obviously to improve purchasing power. Consideration of this, however, would lead to a very complicated discussion of socio-economic problems beyond our terms of reference. The short-term policy essential on health grounds should be to extend the activities already in operation, especially in respect of protective foods, and to subsidize consumption by low income groups, particularly expectant mothers and pre-school children within these groups." An account of the substance of this report is given by A. R. Paterson, in the *East African Medical Journal*, 1945, July, v. 22, No. 7, 204.]

Charles Wilcocks.

Colchester, T. R. **Social Services for Africans in the Nairobi Municipality, Kenya.** *Oversea Education.* H.M. Stationery Office. 1946, Jan., v. 17, No. 2, 254–6.

Schüffner, W. Organisation der Bekämpfung der Tropenkrankheiten in Niederländisch-Indien. [**Organization of the Campaign against Tropical Diseases in the Netherlands East Indies.**] Reprinted from *Ein Querschnitt durch die neueste Medizin dargestellt von ihren Schöpfern* [Adam, C., Editor]. *Veröffentlichungen d. Berliner Akad. f. ärztl. Fortbild.* 1940, No. 6, 145–64, 16 figs.

Orkney, Jean M. **The Health of Indian Women and Children.** *J. Ass. Med. Women in India.* 1944, Feb., v. 32, No. 1, 5–16.

The author, who is exceptionally well qualified to deal with the subject, shows that the standards of health of Indian women and children are even lower than those of the population as a whole.

A few figures will suffice to illustrate the distressing wastage of life and health that still occurs. Corresponding figures for females in England and Wales are shown in brackets.

The expectation of life for Indian females in 1930 was 26·56 years (62·67 in 1931). The specific death rate for females in British India in 1930–32 at the ages 15–19 was 10·6 (2·3) ; and at the ages 20-29 it was 11·9 (2·9).

The maternal mortality rate for India is not accurately known, it is estimated as 15–20 (2·76 in 1941). The wastage of life is most pronounced in early life, of all the deaths occurring in British India, the percentage among children under ten years is 48·5 (10).

The causes of the low level of health of women and children are discussed under the heading of social security, education, and organized public health. Details are given to show how utterly inadequate is the supply of medical women and health workers, and a plea is made for the extended use of instruction in hygiene among teachers and schoolchildren.

A brief reference is made to the population problem ; it is stated that : " A continuous adjustment between the population and the resources available will be needed, and constructive thought must be given to the means of making these adjustments," but no suggestion is made for the inclusion of the subject in the sphere of action of the public health department.

In a nutritional survey in an urban area at least 38 per cent. of the mothers were found to be " malnourished " ; and in a group of 284 infants, 168 under the age of six months were in a good state of nutrition, but when they had reached the age of one year only 31 could be placed in this category.

John W. D. Megaw.

United States Navy. Bureau of Medicine & Surgery. **Epidemiology of Diseases of Military Importance in the Netherlands Indies, including the Identification and Distribution of Arthropods of Medical Importance.** [Navmed 133.] pp. vi+ 250, 19 figs. (maps), & 1 pl. [Bibliography.] 1944. Washington : U.S. Govt. Printing Office. [40 cents.]

Gunn, D. L., Kirk, R. L. & Waterhouse, J. A. H. **An Improved Radiation Integrator for Biological Use.** *J. Exper. Biol.* 1945, Dec., v. 22, Nos. 1/2, 1–7, 3 figs. [10 refs.]

The authors describe laboratory work with radiation integrators, which are instruments designed to sum up the amount of radiant heat received over a period.

A good many years ago Buxton was engaged on the study of climate in relation to insects. It was well known that radiation of many wave lengths is of very great biological importance, but difficult to measure by any existing apparatus. He endeavoured to produce a relatively simple instrument and was prepared to be content with a relative figure, even if it had been impossible to reduce the readings to some such units as gram-calories per unit of area and time. He produced an instrument which consisted essentially of a black bulb *in vacuo*, full of a volatile liquid and exposed to the sun : it was connected to a burette, which was at shade temperature. Radiant heat from the sun falling on the black bulb heated it and caused the liquid to distil from the bulb into the burette. With this instrument he showed that there were large seasonal differences in the amount of radiant heat received at different seasons in the Samoan islands : these differences were not shown by shade temperature owing to the thermostatic effect of the surrounding ocean.

The present authors have had the use of Buxton's original apparatus and have evolved improved types which can be made in a more nearly standardized manner. They have calibrated these instruments in the laboratory with a source of radiant heat and a pyrheliometer, and they have developed the theory and made some approach towards obtaining absolute measurements.

An apparatus of this type has the advantage that one can control its sensitivity by altering the volatile liquid. The present authors find that if the instrument is exhausted and filled with water, the amount of distillate is relatively small, so that the instrument can be read once a day to give a mean daily intensity of sunshine. If it is filled with alcohol, which is much more volatile, it will give a measure of differences of intensity over much shorter periods.

It seems evident that radiant heat is an important and neglected element of climate. And it seems that this instrument is a simple one which could be set up and used in almost any meteorological station. We look forward to hearing results from tropical Africa, which these authors will shortly be publishing.

P. A. Buxton.

BOOK REVIEWS.

Montel, M. L. R. Memento thérapeutique du praticien colonial. [A Tropical Practitioner's Guide to Treatment.] 118 pp. 1945. Paris: Masson et Cie, Editeurs, 120 Boulevard Saint-Germain. [100 fr.]

The author of this book has had nearly 40 years' experience of practice in the tropics and he holds the position of Medical Officer in charge of the Saigon Polyclinic where "more than a thousand patients daily present themselves for treatment." Therefore, as Professor Brumpt says in his prefatory note, no one is better qualified to write a work on colonial medical practice. The author claims that this work is a "concise précis of therapeutics for colonial practitioners." He has intentionally omitted all history and discussion of the mode of action of medicaments and has made choice of such drugs only as he has found efficacious, omitting also all references to the literature. In his introduction he states: "The colonial practitioner finds himself nearly every day confronted with emergencies and his intervention must be active, energetic and prompt;" he ends by saying that this work is a "résumé, as complete as possible, of the colonial practitioner's therapeutic armamentarium." These are very definite claims and it is only right that we should test them and see how far they are made good, for a pocket manual, if it is to serve its purpose of an aid in emergency, must be accurate and precise in its information and is none the worse for being to a certain degree dogmatic.

It is to be feared that those who expect all this will be disappointed. There is much that is good, but often the information which will be looked for is too vague to be of any help in emergency. Let us mention the good points first. The information is precise and helpful on the following subjects: dysentery, both amoebic and bacillary (though not many British practitioners will endorse the opinion that three pastilles a day of dysentery vaccine *per os* for three days are of much benefit in bacillary dysentery); ankylostomiasis, schistosomiasis, kala azar, leprosy (though it is news to the reviewer that enuresis in infants should make one suspect leprosy), opium poisoning, malaria (an excellent summary), sprue (but undue stress is laid on the action, or failure of action, of the pancreas), tetanus, tinea imbricata and African trypanosomiasis.

Next, to justify our statement that the information is often too vague to be helpful we may cite the following: *Actinomycosis*. "Sulphonamides, dagenan, thiazamide as adjuvant to the classical treatment." One is then referred to Blastomycosis and finds: "iodine internally and externally; auto- and hetero-vaccines by injection, by ingestion, on dressings; brewer's yeast, penicillin." A mere list such as this, without a word as regards dosage, is not of much service. Again, under *Yaws*: "I use bivatol, muthanol and quinby alone or together with sulpharsenol, acetylarsan and stovarsol," nothing as to dosage or mode of administration. Under *Strongyloidosis* again merely a list: thymol, ethereal extract of *Filix mas*, chenopodium may be tried, and quinacrine, stannoxyl, gentian violet, methylene blue by mouth or intravenously, arsenobenzene intravenously and antimonials. Many more examples of this vagueness might be cited, but these will suffice.

Insolation is very poor; nothing is said of the various forms of heat trauma and their different treatments. *Xerophthalmia* is dealt with in three lines under the complications of malaria. The author mentions that in *dengue* there occurs a swelling of the kidneys to such a degree that it is perceptible by renal ballottement and may even lead to the possibility of operation being undertaken for renal tumour. *Rabies* is not referred to at all. There are a number of misprints; among them D.D.T. and D.T.T. are used impartially.

The subjects are dealt with in alphabetical order, so there is no pressing need for an index, but it will be gathered from what has been said that the work is

difficult to place and, in spite of its good points, the defects are such that in its present condition it cannot be unreservedly recommended as meeting the needs of the tropical practitioner. *H. Harold Scott.*

GHOSH, Birendra Nath [M.B.E., F.R.F.P. & S. (Glasg.), F.R.S. (Edin.), etc.]. **A Treatise on Hygiene and Public Health with special reference to the Tropics.** Eleventh Edition. pp. xvi+707, 161 figs. 1945. Calcutta: Scientific Publishing Co. [Rs. 12/8 or 21*s*.] [Review appears also in *Bulletin of Hygiene*.]

This, the eleventh, edition of Ghosh's *Treatise on Hygiene and Public Health* appears in less than two years after its predecessor, an interval shorter than that between any two previous editions. We do not know, of course, the size of the editions, but the fact alone bears witness to the popularity of the work. Its merits have been repeatedly extolled in reviews of earlier editions in this *Bulletin*, so there is little to add now. The issue of eleven editions in less than 33 years is recommendation enough of its usefulness to public health officials, to teachers and pupils alike. The work purports to have special reference to the tropics, but only a very small part—in particular, the appendices and a chapter on Diet in India—is not applicable to temperate climates equally. In short, most of the work is of general application, though the tropical aspect is kept in view.

There are two additional chapters in the new edition, one on Camp sanitation—a short chapter, but all the essential points are dealt with, such as choice of site, the general lay-out of the camp, the securing of a safe and ample water supply and the questions of food and cooking and disposal of refuse. The second addition is a chapter on Social Medicine, written by Dr. J. B. Grant, Director of the All-India Institute of Hygiene and Public Health, to whom due acknowledgment is made in the preface.

In a book so excellent and in which so much is included, it comes as a surprise not to find any mention of manganese among industrial poisons, considering the number of important papers on the subject which have appeared in the last five or six years; also, in work having special reference to the tropics one would expect to see some account of infantile beriberi (which is not the same as beriberi in infants) and of Dr. Fehily's work in this connexion. Another disease one misses is sprue and one looks in vain for something about human cysticercosis and hydatid. In fact, the only remarks on *Echinococcus* are the brief statement on slaughter-house rules that "Dogs and rats should not be allowed around the slaughterhouse on account of the danger of *trichinosis* and *echinococcus* disease." (p. 102) and "*Echinococcus granulosus* is found in the cystic or intermediate stage in the liver and other parts" (p. 415). Under venereal diseases nothing is said of lymphogranuloma inguinale, or granuloma venereum or of bejel. No mention is made of the association between herpes and varicella.

So much for omissions; one or two mistakes call for rectification. The Black Death did not occur in the 11th century (p. 464), but in the 14th (as stated correctly later, p. 499); the discoverer of *T. cruzi* was not Chaga. If the author has any grounds for perpetuating in edition after edition that "a second attack [of yellow fever] within two years is not uncommon," he ought to produce evidence for a statement totally at variance with the views of those who have had extensive experience of this disease.

Finally, a suggestion. It would be a great help to students if the degree of magnification was stated of the worms and insects depicted. From the illustrations one would gather that *Gastrodiscoides hominis* is much larger than *Fasciolopsis buski*, instead of being one-fourth the length, and *Fasciola hepatica*

is depicted as being several times as large as *Fasciolopsis buski*. Among the insects the house-fly is depicted as being larger than *Stomoxys*, while *Simulium*, *Stomoxys* and the tsetse fly are all about the same size.

All these are points which could easily be put right and the book remains one to be heartily recommended and, in these days of expensive books, is remarkably cheap. *H. Harold Scott.*

Moll, Aristides A. [Ph.D., Secretary-Editor of the Pan-American Sanitary Bureau, Washington, D.C., etc.]. **Aesculapius in Latin America.** pp. xii + 639, numerous illustrations. 1944. Philadelphia & London: W. B. Saunders Co. [$7.]

As Secretary-Editor of the Pan-American Sanitary Bureau, Washington, the author has access to the best medical libraries in the world and he has utilized his opportunities to produce a work of the utmost, one might justly say of unique, interest. Interesting books may be said to belong to one of three categories: (1) Those which may be read continuously from start to finish and which hold one's attention and interest to the end. Often their permanent effect is slight and the work is soon forgotten. (2) Those which produce a more permanent impression and which we turn to and read again more slowly and with greater attention. (3) Those to which we may have to refer in the future and therefore keep always at hand.

The present work by Professor Moll is, if not unique, very exceptional, for it partakes of the characters of more than one of these categories, perhaps of all three. To review it really adequately would occupy a whole issue of this *Bulletin*, and mere enumeration of the titles of its 78 chapters would fill all the space available for review. We can, therefore, only touch upon a very few points and, otherwise, speak in general terms.

The author has dealt with this colossal subject in two main divisions. In the first he writes of times up to the end of the 18th century, and in the second from this to the present day. Few people are aware of the richness of the New World in vegetal medicinal plants, among them, to name only a proportion, are cannabis indica, carpotroche, cascara sagrada, chenopodium, coca, guaiac, ipecacuanha, jaborandi, jalap, krameria, sarsaparilla, and, above all, cinchona, and there is little doubt that the American natives were well acquainted with the uses of many of them, their toxic properties, their use as diaphoretics, as cathartics, emetics, haemostatics and laxatives. They practised bleeding, administered enemas, applied poultices, made splints of plaster and gums, and performed trephining, amputations and other surgical operations. Enlightenment had advanced even to the stage of euthanasia for incurables—though euthanasia would seem to be a euphemistic term and a more merciful method might have been found than breaking the back of the unfortunate patient. Cortés had so high an opinion of the skill of native doctors that, in a letter to King Charles V, he stated that there was no need to send out doctors from Spain. It was thought by many that disease could be got rid of by passing it on to someone else, an idea which prevailed in England at least as late as the beginning of the present century, when it was a common belief among men with gonorrhoea that they would be cured by passing the infection on to some unsuspecting virgin. It is said that Averrhoes in 1553 described the circulation of the blood and that Servet (1535), Lobera (1542), Valdés de la Plata (1545), Montaña (1551) and others were also precursors of Harvey, and Gonzala wrote on *bubas* (yaws) in 1526.

In public health also they went far. The rulers of the Incas made provision at public expense for relief of the poor, for cripples, for the blind and the aged, and in 1524 an ordinance by Cortés required human waste products to be

removed from houses, and streets to be cleaned ; discharge of domestic waters into the streets was forbidden and all slaughtering of animals had to be done outside the cities. As long ago as 1513 persons were appointed in Porto Rico and Santo Domingo to keep records of births and deaths. After these general matters the author passes on to autochthonous diseases, epidemics, quarantine, early medical practice and hospitals.

In the second part, designated The Independence Period, the author discourses of the developments in medicine and surgery and their various branches and the teaching of them—botany, pharmacy, dentistry, paediatrics, obstetrics, public health, and the rest. A chapter, all too short, is devoted to medical martyrs, many of whom died as a result of attending cases of typhus and yellow fever ; the story of Oroya fever, Verruga peruviana, and Carrión's tragic death is included. The whole work is embellished by numerous illustrations and portraits. There are two invaluable Appendices, one a chronology of disease, taking each in turn ; the second a medical and general chronology for Latin America from 1492 to 1943. There is an abbreviated selective bibliography, and there are indexes of names and of subjects.

There are two things which detract somewhat from the great value of this work. First, over-condensation in attempting to get so vast an amount of information into so small a space has resulted in the narrative becoming at times little more than a catalogue of names, whole pages here and there consisting solely of names and dates. Second, the irritating interposition of footnotes on almost every page, whereby the continuity of reading is repeatedly interrupted. Delightful though the book is, it would be even more readable if the information were less condensed and the footnotes were incorporated in the text. Perhaps it is not too late to urge the author—for fresh editions are certain to be called for soon—to divide the work into two, or even more, volumes. There is sufficient material for half a dozen at least, each as large as this one ; reading would be facilitated and the information would be more easily absorbed if accounts were fuller, for nearly all the chapters could be much amplified with advantage. Interest would be still further enhanced if more detailed biographies were given of some of the hundreds of persons referred to in the text as men of note.

These are just suggestions and do not detract from the great debt which medical practitioners in the tropics and medical historians everywhere owe to the author for this splendid piece of work. *H. Harold Scott.*

Craig, Charles Franklin [M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel, U.S. Army (retd.), D.S.M., etc.] & Faust, Ernest Carroll [M.A., Ph.D., etc.]. **Clinical Parasitology.** 4th Edition, thoroughly revised. 871 pp., 305 engravings & 4 coloured pls. 1945. London : Henry Kimpton, 25 Bloomsbury Way, W.C.1. [50*s.*]

The fourth edition of this now famous book is bigger than its predecessor by 104 pages, yet it remains a handy volume. The print is the same as before, the paper is good, and the illustrations excellent. Apart from additions in the general text, there is a new chapter, on the geographical distribution of parasitic infections, and in relation to each important parasite there is a separate section on pathogenesis, which is a new feature. The book, of course, is more than a treatise on the morphology and life-history of the parasites, it contains, as before, information on the pathology of the relevant human diseases, their symptomatology, treatment and control. During the war much new information has been acquired on the subjects with which the authors deal, and in most important respects this new information has been incorporated if it was

available in time. The authors have been closely associated with the teaching of these subjects during the war, and have evidently been alert to receive new information.

For instance, the dry and moist forms of oriental sore, recently described in Russia, are mentioned, Bullis fever and Colorado tick fever are described, the use of DDT for many purposes, and the trials of hyper-immune rabbit serum in the treatment of Rocky Mountain spotted fever and of *p*-aminobenzoic acid for typhus, are referred to adequately, in so far as information was available at the time when the manuscript must have been sent to press. The sections on African trypanosomiasis and *Glossina*, however, could be improved. The descriptions of the haunts and habits of the various species of tsetse flies, and of methods of control, are inadequate. The importance of *G. tachinoides* and *G. submorsitans* in transmission, and the difference in the control methods for the river-haunting and the non-river-haunting species, are by no means sufficiently stressed. There is no clear statement of the fact that infections with what is usually regarded as *Trypanosoma gambiense* may be as acute as those due to *T. rhodesiense*. Is the remark that *T. gambiense* may be transmitted by coitus worth retaining?

The section on the vectors of malaria is good; now that *Anopheles punctulatus punctulatus* has been added, all the important species have been included with the exception of *A. melas*; but the breeding places of *A. gambiae* (as stated in the table on pp. 642, 645) give a poor picture of the habits of this mosquito. The vectors of yellow fever are well recorded, and, in fact, throughout the book the lists of vectors and intermediate hosts are very comprehensive. Two small points (page 371) may be mentioned, *Mansonioides longipalpis* and *M. annulipes* are synonyms, and the water plant is *Pistia stratiotes*, not *stratioides*.

Clinical Parasitology is to be recommended as a reference book and as a textbook, to teachers, research workers and students alike; it is of the very highest quality. *Charles Wilcocks.*

Biesheuvel, S. [M.A.(Cape Town), Ph.D.(Edin.)]. **African Intelligence.** pp. viii+225, 12 figs. 1943. Johannesburg: South African Institute of Race Relations, P.O. Box 96. [7*s.* 6*d.*]

The title of this book is a sufficient indication of the importance of the subject with which it deals. Whether we start with certain prepossessions about the intelligence of the Africans, or with none at all, we must admit that as an academic, and as a practical issue, it is one of the most important of our day. It should be noted at once that "African" in this sense means only Africans in the Union of South Africa. No other Africans are referred to in this study, and readers who know other parts of Africa have to be constantly checking their reactions to some of the statements and reminding themselves that this is a study in a strictly limited field.

The book originated, as the author explains in his preface, from an attempt to review a monograph by Dr. L. Fick of the South African Council for Educational and Social Research on "The Educability of the South African Native." Fick's main contention was that the mental age of the Africans in the Union was from 4–5 years below that of the Europeans, and that the observed inferiority was permanent and innate, and not due to preventable environmental influences. Dr. Biesheuvel found that a critical examination of this monograph raised so many issues that he had to deal systematically with each problem. Hence his review grew into a book which has all the freshness and drive of a challenge, and yet has preserved an essential scientific objectivity. He achieves this by relegating to his final chapter any detailed analysis of Fick's work, and by concentrating all the rest of his book on an examination

of the issues involved in comparisons of intelligence on an inter-racial basis. It is unfortunate that there is no index to this otherwise well-documented work.

In a brief survey of the leading authorities on the nature of intelligence, he lays down as an essential preliminary that " any study of African intelligence, particularly if the comparison with the intelligence of Europeans is its chief object, will have to make some choice between the different theories of intelligence now in the field." Arising out of this as a starting point, he asserts that intelligence test scores are on the whole of less importance than mental processes and their attributes and antecedents. Two practical issues are then stated, which recur in different forms throughout the book, and which are of far wider import than their occurrence in the Union of South Africa—the formulation of educational policies for Africans; and the adjustment of Africans to, and their future development in, western civilization.

The main chapters of the book fall into two parts. The first deals with the measurement of intelligence, the problems of sampling, the effect of the cultural milieu on test-intelligence, and the suitability of existing tests for measuring African intelligence. The second half reviews the factors of home environment, school and nutrition in their effect on intelligence.

In the earlier chapters there are two leading scientific problems which are of wide interest. The first is the question: what do intelligence tests measure? Dr. Biesheuvel's answer is " We are compelled, therefore, to look upon an intelligence test score, not as a direct measure of innate ability, but as a measure of hereditary potentiality as it happens to have been realized by specific environmental circumstances." The latter half of the book is, from this point of view, an examination of selected environmental circumstances, analysing their effect on the growth of intelligence. The second main problem is that of the control group. Dr. Biesheuvel considers that in previous inter-racial intelligence studies in South Africa, control groups have been chosen where the factors of nutrition and home and school environment have not been equalized. He raises indeed the question of whether the environmental differences are not so great between Africans and Europeans in the Union that the matching of two representative and parallel groups is impossible. He shows how difficult it is to select representative samples of the African population, which cannot be done with any accuracy on a basis of division into urban and rural, tribal and detribalized. He discusses such difficulties as the unfamiliarity of the Africans with the test situation, and the speed factor in the tests which is based on a peculiarly Western European sense of time and " hustle ". His conclusion at this point is that current attempts to measure inter-racial intelligence are premature, and all further work on these lines will inevitably be unscientific until further research has been made into the " abilities, response mechanisms and manner of thinking and feeling of the Africans." Two examples of such research by Nel and Endeman, which he quotes and commends, are both unfortunately published in Afrikaans, and are therefore virtually inaccessible for consultation by most medical and educational research workers outside the Union.

In examining the effect of home environment on the growth of intelligence, the research worker in the Union is placed in a peculiarly difficult position. As Dr. Biesheuvel points out, African tribal family life develops intelligence in directions almost entirely different from those of the European home. The home environment in tribal society conditions the growing child to become a member of a group, where formerly the standards of skills, ability and behaviour were laid down by tribal codes and sanctions. In certain remote parts of Africa such tribal society can still be found, but it does not exist anywhere in the Union in an untouched form in spite of the policy of segregation. White

and black society are bound together by economic links which stretch from the towns and industrial centres into the interior of the reserves. Hence in the Union there can be no measurement of intelligence as developed under purely tribal conditions to serve tribal purposes. Dr. Biesheuvel decides on other grounds that tribal Africans will have to be excluded from the experimental group, for the reason that there can be no parallel European control group with which to compare it. But a very fundamental difficulty then arises. In comparing the home environment of urban Africans with urban Europeans many of the material features of the home may have certain similarities, but the general cultural milieu in which the African child is brought up in the cities is neither African nor European. It is a hybrid culture which has not yet been sufficiently studied in any of its aspects, sociological, economic or psychological, so as to provide accurate factual data for measuring home environmental factors. Dr. Biesheuvel says emphatically that home environment can only be equated within the same cultural milieu, and it is evident to any social research worker that living in the same city does not necessarily produce a similar cultural milieu. Moreover, his conclusion, after examining such social-economic studies of urban African conditions as are available, is that " the average urban African home environment is bound to stunt very markedly the growth of intelligence of the children reared in it, not only by failing to provide those stimuli which alone would enable the most to be made of innate potentialities, but also by creating situations which have an adverse effect on such growth as might spontaneously occur."

To all workers in tropical areas the relation of malnutrition to the growth of intelligence will be of great interest. Dr. Biesheuvel points out two major difficulties in assessing this particular environmental factor. He considers the clinical method of judging malnutrition as too elaborate for use with large groups, and rejects the height-weight ratio as being discredited. " That leaves us at the present stage without a valid practical method of judging malnutrition." The second difficulty in his view is the inconclusive nature of the evidence that, subject to particular conditions, the growth and function of the nervous system can be impaired by malnutrition. As a result of reviewing a number of authorities, however, he comes to the conclusion that qualitative malnutrition, if severe, permanently impairs intelligence at all age-levels and hence he urges that in measuring intelligence some control should be exercised over the nutritional condition of the experimental group.

The results of diet surveys of Africans in urban areas, though so far not correlated with intelligence testing, show such a general low level of nutrition that comparisons could only be made with the very lowest income levels among Europeans—that is among the most depressed section of the urban European population. This group, as Dr. Biesheuvel says, would be useless for control purposes in an inter-racial study, as it would probably represent a genetically inferior sample of the European community.

The result of this analysis is a somewhat negative conclusion. Dr. Biesheuvel says categorically that " under present circumstances and by means of the usual techniques, the difference between the intellectual capacity of Africans and Europeans cannot be scientifically determined. One cannot environmentally equate an African group with a European group without selecting unrepresentative samples."

It is interesting to note that Dr. Biesheuvel's doubt about the representative character of samples of the African and European population is in line with a conclusion reached in the United States of America. In 1934 the *Journal of Negro Education* gave a whole number (Vol. III, No. 3) to a critical summary of the studies on the relative physical and mental abilities of the American Negro. It was recognised that the difficulty of getting fair samples was one

of major importance, and this difficulty was practically insuperable in the southern States, the area where the racial situation shows the nearest parallel to that in the Union. It was stated categorically that " it is impossible to secure ' fair ' samplings of Negro and white children of the same age who are equally advanced educationally and have had similar environments."

Must we therefore accept a non-possumus ? As far as the Union of South Africa is concerned, the dust of the battlefield obscures the main issues. On both sides, black and white, emotional attitudes will enter into any attempt to make comparisons of intelligence on inter-racial lines. Too much is at stake in such a study, which is directly bound up with the economic and political development of the country. That is no reason, however, why in other parts of Africa studies should not be made of the various environmental influences and their effect on the growth of intelligence, without bringing in the factor of comparison with Europeans. Casual statements are made often about a particular tribe being " so intelligent ". Dr. Biesheuvel himself refers to such a statement about the Basuto, as being " intellectually superior to other tribes." As they are outside the Union politically, though closely linked with it on economic grounds, they have not been included in any of the surveys reviewed by Dr. Biesheuvel. He asks the question, which has constantly puzzled many people in Africa, whether statements about the intellectual superiority of any tribe can be substantiated. He thinks that intelligence tests could be applied to such a problem. Here is an obvious field for a combination of research techniques, for the psychologist will need the help of the sociologist and the doctor in the assessment of the home environment and the nutritional factors. It may be unimportant in the scientific field whether certain tribes are proved, by such tests, to be more intelligent than others. Dr. Biesheuvel thinks that these popular beliefs are unfounded, though, until proof is forthcoming, no one can make positive statements on the subject. What is, however, of great importance in the scientific field is the working out of joint research techniques between psychologists, sociologists and doctors. The problems connected with the development of Africa and its peoples, particularly in the sphere of education and intellectual advance, cannot be solved by a number of unrelated approaches. *Margaret Read.*

HARPER, F. **Extinct and Vanishing Mammals of the Old World.** pp. xv+850, 67 figs. & 1 pl. [Bibliography.] 1945. Special Publication No. 12. American Committee for International Wild Life Protection, New York Zoological Park, New York 60, N.Y. [30*s*.]

The present book is briefly noticed because of the relation of game animals and game extermination to tsetse flies. The volume consists of a relatively brief introduction which explains how the information has been collected and points out the great variety of factors which have caused the disappearance or increasing scarcity of many species of mammal in the Old World. It contains a chronological list showing the approximate dates (generally to a half-century) of disappearance for each continent separately.

The greater part of the book consists of an account of many species arranged under Orders. Some of these species have disappeared or are in grave danger of doing so, but some of them, as it appears to us, are not at the moment greatly reduced or on the danger list. *P. A. Buxton.*

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